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**Investigation on Heart Rate Variability (HRV) and  
psycho-social-affective adjustment in Italian women with  
ovarian cancer.**

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**In Memoria di Gabriella Fiorentino**

A te, Sga, che con la tua forza e passione,  
ispiri la mia vita.



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**PART I**

**THEORETICAL FRAMEWORK**



## INTRODUCTION

The mind body integration applied in an outstanding pathological field as cancer , is the core of this thesis.

Moving between the theoretical framework of Psychoneuroimmunology and Psycho- Oncology, this work tries to evaluate, using quantitative tools, the connection between psychological states (mind) and physiological conditions (body) in a specific sample: women with ovarian cancer. The ultimate aim of this study, is to offer evidences of the effect that illness psychological adjustment may have on the pathology, thus offering practical advice to health professionals on how to handle with cancer.

The choice of women with ovarian cancer was made for two main reasons: first, the nature of this aggressive illness associated with very poor survival and high recurrence rates. It is the most fatal malignancy of the female genital tract and the fourth most common cause of female cancer death. This because it is detected at an advanced stage, with a 5-year survival rate of 46% for all the stages and 31% for advanced stages. Second, the management of ovarian cancer that normally includes radical pelvic surgery and multiple aggressive courses of chemotherapy, worsen the impact of this illness on patients' Quality of Life (QoL).

The thesis includes a single study that answers to some main questions:.

- 1) The study describes, for the first time in the Italian population, the psychological adjustment to cancer, evaluated through the assessment of perceived social support, body image, coping towards cancer and Quality of Life.
- 2) The study evaluates the effective physiological condition, linked to the autonomic balance, as an objective measure of healthy adjustment, recording the basal Heart Rate Variability (HRV).

However, we also tried to identify the connection between mind and body, using scientific methods, trying to underline the existing correlations between psychological adjustment, physiological conditions, Quality of Life and survival.



# CHAPTER I

## PSYCHONEUROIMMUNOLOGY

Psychoneuroimmunology (PNI) is the science that seeks to understand how the exquisite and dynamic interplay between mind, body, and environment relates to behavioural characteristics (Ulvestad, 2012) describing the communication between the brain and the immune system (Pariante, 2015; Fig.1):

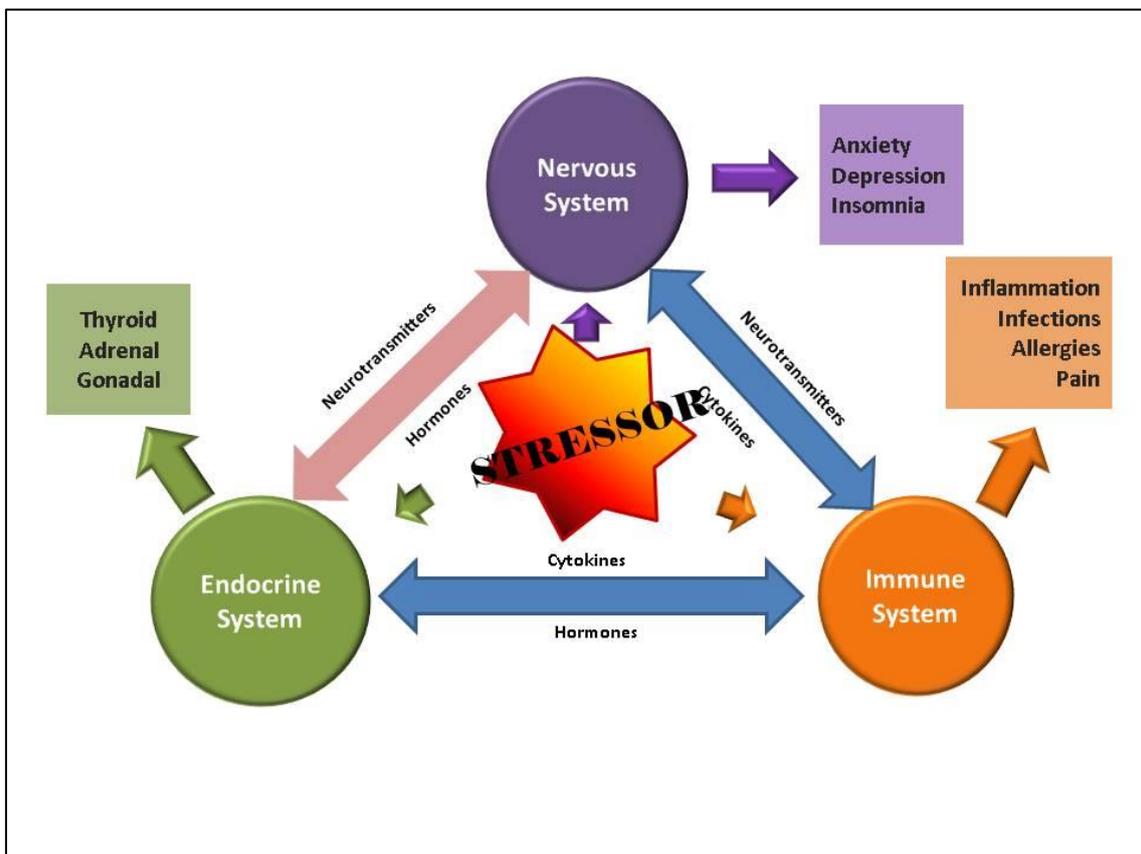


Fig. 1: The PNI network

In 1964 George F. Solomon coined the term psychoimmunology and published a landmark article: “Emotions, Immunity, and Disease: A Speculative Theoretical Integration” (Solomon & Moos, 1964). However, despite the importance of this inaugural conceptual article, only a handful of human studies appeared prior to the 1980s.

To that date, there are the first massive publications about PNI, defined as the science which demonstrates the so-called “Great Connection” (Bottaccioli, 1995). As a matter of fact, PNI, along with neuroscience, shows that the brain, cannot be just considered as a processor, but it should be considered as an endocrine gland, thus retrieving some ancient concepts as Hyppocrate’s “the brain is a gland, just like the breast”. In PNI approach, the immune system is seen as a sensory organ, an inner eye organized in networks aimed to internal and external surveillance (Bottaccioli, 1995).

In particular, PNI emphasizes the active interactions between the immune system (IS) and the hypothalamus–pituitary–adrenal (HPA) axis or the sympathetic nervous system (SNS), and the role of peripheral and central cytokines as mediators of these interactions. Undoubtedly IS is a physiologic homeostatic system that, within certain limits, contributes to the constancy and integrity of the organism. However, a source of confusion could be that while immune responses are physiologic responses expected to be maximally efficient during infectious/inflammatory diseases, they sometimes contribute to pathology (Besedowsky & del Rey, 2007).

The PNI highlights that human organism works like an integrated network that unifies organs and systems. In this network, there are the same codes and a common language. Both if the message starts from cerebral circuits activated from emotions, thoughts, autonomic activation, and if it starts from endocrine or immune organs, each component of the network will read it and will answer to it (Bottaccioli, 1995)

Many studies, up to date, have been conducted on Psychoneuroimmunology (PNI), and this field can be seen as a catalyst in biobehavioral research in cancer, highlighting the neuroimmunological paths through psychosocial factors as stress, pain, loneliness can effect on disease outcome (Goncalves, 2015)

However, how does the “Great Connection” work in cancer?

## **1.1. From Macroenvironment to Microenvironment**

Cancer recent research pointed out some new evidences on cancer biological dynamics, identifying the importance in its origin and metastatic pathway of the so-called “tumor microenvironment”, the set of heterogeneous non cancer cells involved during the course of multistep tumorigenesis (Cancer Stem Cells, Immune Inflammatory Cells, Cancer Associated Fibroblast, Endothelial Cells, Pericyte) as in Hanahan & Weinberg, 2011 . The “Hallmarks of Cancer” have been identified including sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. These hallmarks seem to be fostered by inflammation and by its components as cytokine, chemokine, macrophages and leucocytes (Hanahan & Weinberg, 2011; Gonda & Wang, 2009; Solinas et al., 2009; Medrek et al., 2012; Pitroda et al., 2012).

Research also focused on the “Macroenvironment” , meant as life context of the cancer patient. Evidences have been collected of the causal role stressful life events (Chida et al., 2008) and depression (Satin et al., 2009; Pinquart & Duberstein, 2010) should have on higher mortality rate in patient with cancer different for site and type.

Thus becomes evident the presence of a model of impact of psychosocial stressors able to modulate tumor microenvironment, and through this, cancer progression (Goncalves, 2015). The downstream activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, could exerts selective physiologic pressures that initiate molecular signaling pathways involved in cancer hallmarks (Hara et al., 2011; Lutgendorf & Sood, 2011; Cole & Sood, 2012).

In order to achieve ultimate evidences of the influence “Macroenvironment-Microenvironment”, experimental trials were conducted on animal models (mice and rats). Human cancer affections (ovarian, skin, colon) were studied, making it possible to artificially increase chronic stress highlighting the effects of stress on tumor growth (Thaker et al., 2006;Sood et al., 2010) and enrich the environment, showing its link to decreased cells proliferation and thus decreased tumor growth (Cao et al., 2010).

### *1.1.1 Glucocorticoids*

A chronic and unrelenting stress, with an insufficient perceived social support, can deregulate functioning glucocorticoids pathway (Volden & Conzen, 2013).

In clinical trial “in vivo” on different solid tumor cells (brain, breast, colon, ovary and others) has been observed that pharmacological GCs hormone (i.e. Cortisone) administration could stimulate anti-apoptotic gene expression and antagonize the ability of cancer cytotoxic treatments to induce cell death (Zhang et al., 2007).

An experiment conducted on rats genetically prone to mammary tumor formation, the social environment influence on cancer progression and malignancy was examined. Isolated animals did develop significant dysregulation of cortisol responses to everyday stressors. Corticosterone response to an acute stressor was enhanced and recovery was markedly delayed, associated with increased mammary tumor progression (Hermes et al., 2009).

Flattened cortisol circadian levels in metastatic breast patients, might be related to tumor burden and linked to specific psychological conditions (Volden & Conzen, 2013). In presurgical breast cancer patients, distress and avoidant coping were related to flattened diurnal cortisol rhythms; given that, circadian cycles regulate tumor growth, this could highlight possible psychosocial effects in cancer-related circadian disruption (Dedert et al., 2012).

GCs effect on tumor progression also through the microenvironment, affecting tumor-stroma cells, with a notable role in tumor invasion and migration (Smith et al., 2007; Hidalgo et al., 2011). GCs also influence tumor progression deregulating immune system (Costanzo et al., 2005) and systemic metabolism (Kaidar-Person et al., 2011).

### *1.1.2 Catecholamine*

Catecholamine (Epinephrine, Norepinephrine, Dopamine) affect almost each phase of the metastatic cascade. **Angiogenesis:** In a model of orthotopically xenografted human ovarian tumors in nude mice, a tumor growth-promoting effect was observed in animals following exposure to chronic stress; this increase in tumor growth was associated with the up-regulation of VEGF, a pro-angiogenic cytokine, in tumor tissues. In vitro studies also demonstrated the NE-mediated secretion of VEGF by ovarian carcinoma cells. In

addition, studies have also indicated that NE induces a significant increase in the synthesis and release of other pro-angiogenic factors, including IL-6, other important cytokine (Basu & Dasgupta, 2013). **Invasion:** in vitro cell migration studies showed that NE is a potent inducer of migratory activity in carcinoma cell lines of colon, prostate, ovarian cancer cells and breast tissue origin, and this finding has been confirmed in a mouse model. Cell migration is mediated by adrenergic receptors and the beta-blocker adrenergic receptor antagonist drug (Powe et al, 2010). **Anoikis:** in animal model of prostate cancer, E activate an antiapoptotic signaling pathway (Hassan et al., 2013). However, DA can induce apoptosis, as shown in in vivo and in vitro ovarian cancer cells (Armaiz-Pena et al., 2013). **Immunity:** Catecholamine could effect on the immune system, reducing type1 cytokine, T cells and natural killer cell activity, enabling tumor cells to avoid elimination (Armaiz-Pena et al., 2013).

### *1.1.3 Inflammation*

Pro-inflammatory cytokines, as IL-6 secreted after a stressful interaction, play a key role in cancer progression and could be a prognostic indicator of survival and metastasis (Powell & Sheridan, 2013).

A trial on animal model of human cancer (colon and mammary) showed that a functional impairment in immune system related to myeloid-derived suppressor cells (MDSC ) inhibit immune cell responsiveness to anti-viral/tumor interferon, that directly inhibits tumor growth and coordinates anti-tumor innate and adaptive immunity (Mundy-Bosse et al., 2011). In a randomized clinical trial on patients with breast cancer, individual with higher level of psychosocial stress, showed significant alterations of MDSC and higher levels of circulating IL-6, with an evidence of higher cancer recurrence than control (Mundy-Bosse et al., 2011). Moreover, IL-6 seems to effect on Central Nervous System (CNS); in patients with epithelial ovarian cancer, higher level of IL-6 produced in ovarian carcinomas microenvironments, elicited sickness behaviors in the CNS, contributing to depressive symptomatology, thus creating a negative feedback loop (Lutgendorf et al., 2008).

## 1.2 Balance in a Breath

David L. Felten (1991) was the first to discover the anatomical connections between CNS and IS. He wrote, “ We documented how stressful events can be associated to negative effects on health and to a weakened immune response; unluckily, a few attention has been paid to the scientific examination of the counterpart, how positive emotions can produce positive effects, for health and for a more powerful immune response. [...] Can joy, a strong personal and social support, persistence and crossing over difficulties help the patient to get out from an immune-mediated disease or prevent a relapse?” (Felten, 1991; Bottaccioli, 1995).

In more than 20 years of scientific research, this question has been partially answered, in particular through the discovery of an important physiological index: the Heart Rate Variability.

The Heart Rate Variability (HRV) consist of the changes in the time intervals between consecutive heartbeats (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Fig. 2).

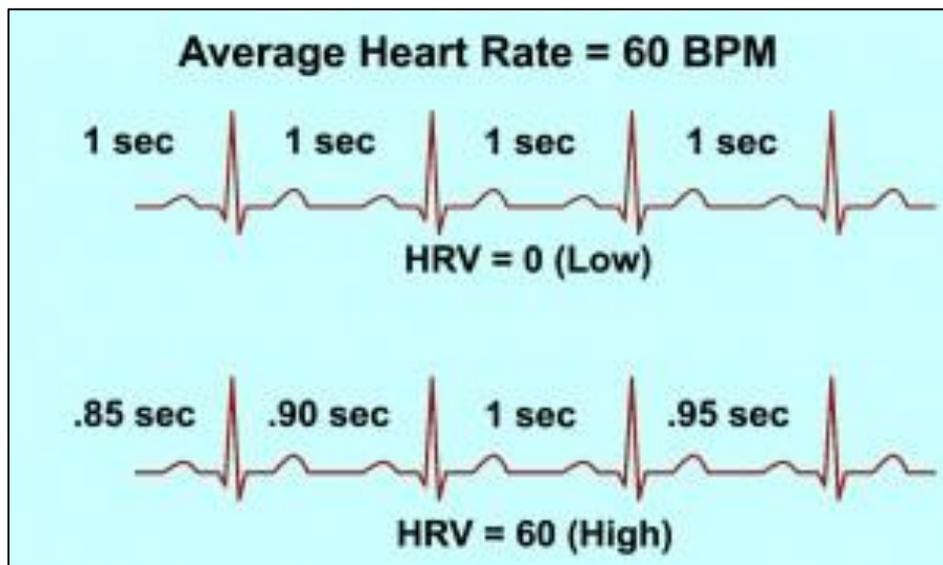


Fig. 2: Heart Rate Variability

HRV can serve as signal markers for various physiological or pathological events e.g. unplanned remission for geriatric patients, infections in critically ill patients and risk of myocardial infarction (Ahmad et al., 2009; Buccelletti et al., 2009; Chiang et al., 2011).

HRV is modulated by multiple regulatory mechanisms that operate on different time scales; the 24-hours HRV recording is produced by the interaction of circadian rhythms, core body temperature and metabolism. The short-term measurement (i.e. 5 minutes) recording is produced by autonomic, cardiovascular and respiratory system, becoming a valid marker of parasympathetic cardiac vagal control and reflecting the status of the autonomic nervous system (Schaffer & Venner, 2013).

HRV can be detected using two different domains: Frequency and Time. In the Time domain, the amount of variability in the interbeat intervals (IBI) between successive heartbeats is quantified in six indices (SDNN, SDRR, SDANN, pNN50, HR Max-HR Min, and RMSSD; Tab.1):

**Tab. 1: HRV time domain indexes and mechanisms (Schaffer & Venner, 2013)**

<b>Index</b>	<b>Mechanism</b>
SDNN/SDRR/SDANN	SNS and PNS
pNN50	PNS
HR Max-HR Min	PNS
RMSSD	PNS

**Legend:** SDNN, standard deviation of NN interval; SDRR, standard deviation of RR interval; SDANN, standard deviation of average NN interval; pNN50, percentage of differences between adjacent RR intervals; HR Max-HR Min, minimum and maximum HR; RMSSD, square root of the mean squared differences of successive RR intervals.

In HRV frequency domain HR oscillation are divided in four frequency bands: ultra-low frequencies (ULF), very-low frequencies (VLF), low frequencies (LF) and high frequencies (HF; Tab.2):

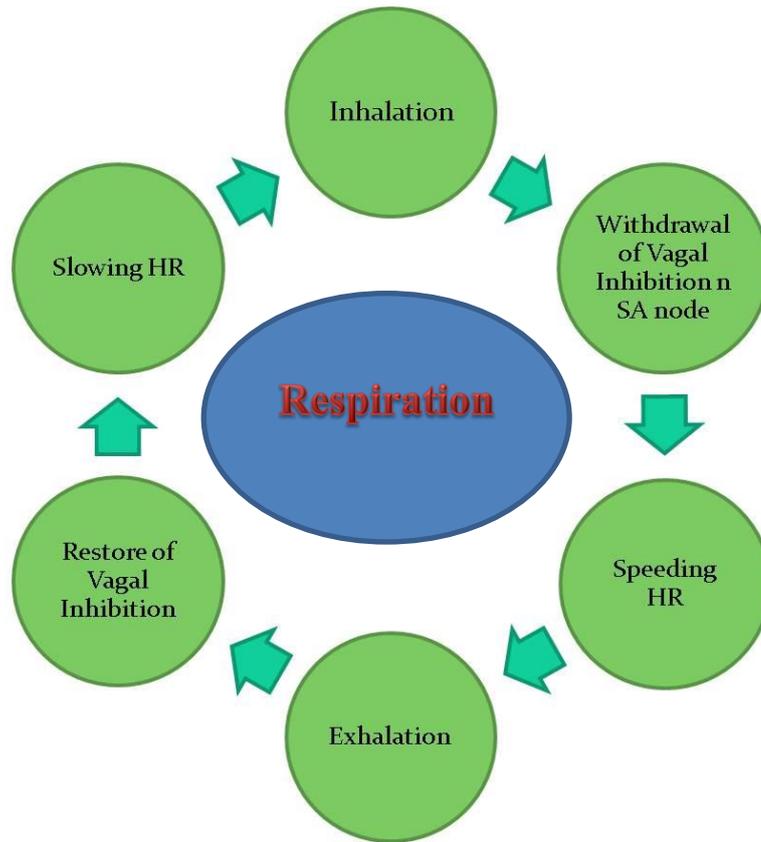
**Tab. 2: HRV frequency domain measurements and processes (Task Force, 1996)**

<b>HRV Band</b>	<b>Processes</b>
Ultra Low Frequency (ULF)	Very slow biological processes (circadian rhythm, metabolism)
Very Low Frequency (VLF)	Temperature regulation, physical activity, PNS and SNS
Low Frequency (LF)	PNS, SNS, baroreflex activity
High Frequency (HF)	Respiratory sinus arrhythmia

The ratio of LF to HF is called LF/HF ratio and appears to reflect the dominant ANS branch. If low, it reflects the PNS dominance and can be observed at rest and during “tend-and-befriend” behaviors; when high, it may indicate SNS dominance and prevails in fight or flight behaviors (Schaffer & Venner, 2013).

In healthy conditions, there is a dynamic balance between Sympathetic Nervous System (SNS) and Parasympathetic Nervous System (PNS) on Heart Rate (Schaffer & Venner, 2013). Specifically, PNS influence is predominant at rest, its activation, in fact, can slow down HR of 20-30 bpm, and even briefly interrupt it (Tortora & Derrickson, 2012).

The influence of PNS on HRV implements through the Vagus Nerve, which allows the physiological mechanism of Respiratory Sinus Arrhythmia (RSA). The HR oscillations change in correspondence of breathing; in particular they should be systematically increased during relaxed states and decreased in stress phases (Lehrer, 2013) (Fig.3):



**Fig.3: Respiratory Sinus Arrhythmia Cycle**

### *1.2.1 HRV and psychology*

Emotions are influenced and influence the decision-mechanism (Damasio, 2003) and provide a substrate for social interaction (Keltner & Kring, 1998). Emotions that are expressed with sensitivity to the situational context, in which they unfold, both in terms of timing/occurrence and magnitude, are more likely to facilitate adaptive responses (Appelhans & Luecken, 2006). The emotions that humans experience while interacting with their environment are associated with varying degrees of physiological arousal (Levenson, 2003). The prefrontal cortex and the amygdala, structures involved in emotions onset and regulation, are also strictly linked to the regulation of the ANS balance via the Vagus nerve (Thayer & Sterneberg, 2006).

The role of the Vagus Nerve on heart regulation has been recently analyzed in a new perspective, thanks to the Polyvagal Theory proposed by Stephen W. Porges.

The Polyvagal Theory emphasizes the neurophysiological and neuroanatomical distinction between two branches of the Vagus and proposes that each branch supports different adaptive behavioral strategies (Porges, 2007). The theory articulates three phylogenetic stages of the development of the vertebrate autonomic nervous system. Each stage is associated with a distinct autonomic subsystem or circuit that is retained and expressed in mammals. The systems identified, which through specific physiologic pathways modulate different behaviors, are the Social Engagement System (SES), the Mobilization System and the Immobilization System (Fig. 4):

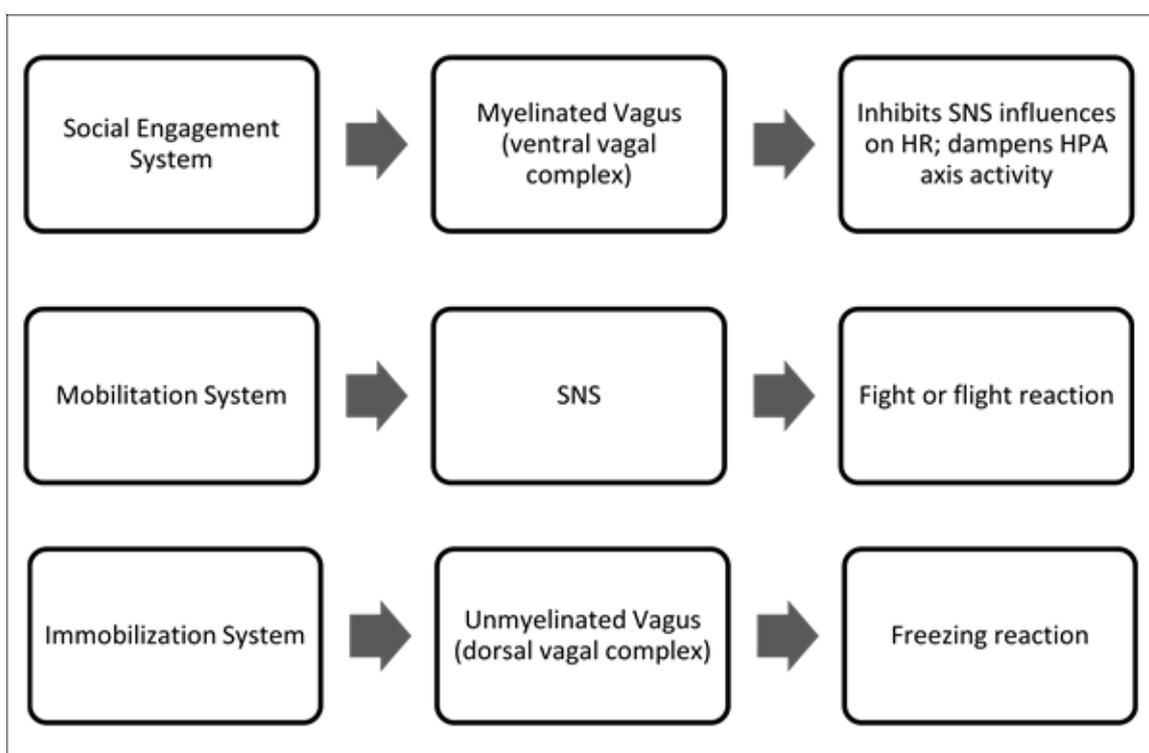


Fig. 4: Systems, branches and responses (Porges, 2009)

In this perspective, the SES plays a key role, consisting of a somatomotor component, which involves visceral efferent pathways that regulate the striated muscles of the face and head and a visceromotor component, involving the Myelinated Vagus that regulates the heart and bronchi (Porges, 2009). This role was defined as “vagal brake”, in which rapid inhibition and disinhibition of vagal tone to the heart can rapidly mobilize or calm an individual. Functionally, the vagal brake, by modulating visceral state, enables the individual to rapidly engage and disengage with objects and other individuals and to

promote self soothing behaviors and calm states, allowing hypothesizing the existence of a Cardiac Vagal Tone (CVT) (Porges, 2007). Thus, a physiological state characterized by increased vagal influence on the heart would support spontaneous social engagement behaviors also through functional and structural links between neural control of the striated muscles of the face and the smooth muscles of the viscera (Porges, 2009).

In healthy population, higher CVT matched with current relationship security, that is the degree to which individuals successfully derive feelings of emotional security within a specific, current attachment relationship (Diamond & Hicks, 2005) and with perceived social support (Schwerdtfeger and Schlagert, 2011). Analyzing stable individual characteristics, still in healthy population, emerged an association between high CVT and increased self-confidence and goal pursuit, without a conscious and intentional intervention (Geisler & Kubiak, 2009). This happens with the habitual use of strategies of emotion regulation that involve executive functions (Geisler et al., 2010) and a higher tendency to habitually employ strategies of stress regulation that likely reduce distress and facilitate social engagement (i.e., engagement coping and seeking social support) with a resulting social well-being (Geisler et al., 2013). Moreover, researchers demonstrated that a lower resting HRV is associated with greater difficulties in emotional regulation, especially a lack of emotional clarity and impulse control (Williams et al., 2015). There is also evidence of a strong relation between higher CVT and fewer depressive symptoms under conditions of high social support, providing crucial support for CVT contribution to decreased depressive symptoms via social processes (Hopp et al., 2013). In animal trials, social isolation induced a significant reduction in CVT, leading also to both depression and anxiety-like behaviors in validated operational tests (Grippe et al., 2007; 2012).

### *1.2.2 HRV and Pathology*

Literature has shown that a meager HRV can be seen as a predictor of generic and specific mortality (Niederer et al., 2013). On the other hand, there is evidence that healthy longevity depends on preservation of autonomic function, in particular, HRV–parasympathetic function (Zulfiqar et al., 2010).

Furthermore, the relation of HRV and specific pathologies has been shown in chronic illnesses, in which a higher vagal tone, registered through HRV, controls the activation of the anti-inflammatory reflex, acetylcholine mediated (Modares, 2013).

In the specific field of cancer, some evidence of the influence of PNS activity on cancer prognosis have been reached. This influence can be understood since Vagal afferents and efferents might inhibit three mechanisms involved in cancer etiology and progression: local oxidative stress and DNA damage, inflammatory reactions and excessive sympathetic responses (DeCouck et al., 2012). In patients with different cancer sites, HRV appears systematically decreased (Kim et al., 2010). However, in male patients with locally recurrent or metastatic cancer (principally lung and gastrointestinal cancer) a higher HRV is significantly associated to survival (Fadul et al., 2010). In patients with cancer who had undergone ambulatory electrocardiogram monitoring for 20 to 24 hours, SDNN was calculated using power spectral analysis. Survival data were compared between patients with  $SDNN \geq 70$  milliseconds (Group # 1) and  $SDNN < 70$  milliseconds (Group #2). Two groups were similar in most variables, and patients in group #2 had a significantly shorter survival rate ( $P < 0.0001$ ). Multivariate analysis showed that  $SDNN < 70$  milliseconds remained significant for survival independent of age, cancer stage, and performance status (Guo et al., 2015). In a large sample of patients with metastatic pancreatic cancer, considered fatal, vagal nerve activity indexed by HRV was independently positively correlated with overall survival and the vagal nerve—overall survival relationship may be statistically accounted by reduced inflammation (DeCouck et al., 2016). Also in women with metastatic breast cancer, vagal activity, indexed by frequency-domain HF-HRV strongly predicted their survival (Giese-Davis et al., 2015). Moreover, in patients with colorectal cancer, high HRV predicts lower levels of a tumor marker, one year later diagnosis, independent of confounders like treatment and cancer stage (Mouton et al., 2012).

Another study showed that HRV parameter, SDNN in Non-Small cell Lung Cancer (NSCLC) significantly predicted poor survival by univariate analysis. However, multivariate analysis revealed that it was not an independent prognosticator for survival in NSCLC patients, even thou it still seems the best variable to monitor patients' general

well-being and ability to perform daily activities (Kim et al.,2015; Greenberg et al., 2015).

Another recent study combined data of five different cancers (colorectal, pancreas, prostate, lung and ovarian) concerning patients' HRV. These data were compared to HRV levels of a healthy sample in another study. The mean HRV of the cancer patients sample was significantly lower (SDNN = 22 ms) compared to the healthy sample (SDNN = 50 ms) ( $p < 0.000001$ ). In particular, women with ovarian cancer in this sample had SDNN= 18.95. These findings are important suggestions for prognostication since they provide expected values of vagal nerve activity in cancer patients. Indeed, low levels of HRV at diagnosis as SDNN below 20 ms, have been shown to predict poor prognosis (DeCouck & Gidron, 2013).



## CHAPTER II

### PSYCHO-ONCOLOGY

Psycho-oncology is considered within the professional practice of psychology, as an example of a subspecialty (Commission for the Recognition of Specialties and Proficiencies in Professional Psychology, 2012). In this taxonomy, a subspecialty is “a focused or narrow field of study within one or more of the recognized specialties” (Nicholas, 2013). The core of Psycho-oncology is to deal specifically with the psychological consequences caused by a tumor. This discipline focuses on the psychosocial and affective concerns of a cancer patient and of his familial environment. This approach, deals both with the psychological consequences of cancer for patients, families and caregivers, and with the possible relationship of psychological factors in relation to cancer development and progression.

The central factors in this approach are the mood, the attitude and the way of dealing with the disease, the stress caused by the event and support social, lifestyle variables and how all these factors connect with the clinical, immunological and hormonal condition.

The main goals in psycho- oncology are (Grassi et al., 2005):

- **Education - prevention:** Campaigns against risk behaviors (such as smoking or food), genetic screening programs, de-stigmatization of cancer and the emotional distress, education about the possible psychological problems, their meaning and their management;
- **Clinical care:** Support for psychological suffering or psychiatry disease onset;
- **Formation:** Educational training in Psycho-Oncology for Health workers and volunteers.

However, the latest goal in Psycho-Oncology is to promote the health of the patient, understood globally (mental and physical), through a multidisciplinary approach to neoplastic disease. In fact, the psycho-oncology is an important example of how

psychology can find its accommodation next to the medical sciences, for a unified understanding of the person suffering from a disease.

Patients and their families need to know that the major emotional problems related to the disease and treatment can be contained and reduced. They should learn to adapt to the new situation of life at all stages of the disease and face the uncertainty of the future. This should be made in order to give meaning to illness, establish a more open communication with family members and health care workers, improve the Quality of Life and foster the ability of the patient to have mastery over his own situation (Bellani, 2011).

The psychological suffering of the patient is also the distress due to the disease, the characteristics of the person who is sick and the family environment, social and cultural context in which it appears.

In cancer, distress is more precisely defined as “a multifactorial unpleasant emotional experience of a psychological, social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, panic social isolation and existential and spiritual crisis” (NCCN Guidelines Version 3. 2015)

The personal level of distress should be assessed, monitored, recognized and treated at every stage of the disease (Grassi, 2005). If the distress is not properly treated, it can lead to significant consequences in terms of psychosocial and physical health. Individual reactivity is an important variable in determining the impact that it could have on each person (Cacace & Cantelmi, 2009).

Psychological support to cancer patients must identify the level and nature of distress, taking into account the many stressors that the individual faces and unexpected adaptations that are followed at every stage of the disease. It is important to assess the psychological state of the patient and consider it in decisions about medical treatments that are appropriate for him. The psychological support is crucial both to address and manage the stressors the patient faces during the illness and for the possible role that

factors of emotional nature can have on the course and, therefore, the prognosis of the disease (as in chapter 1).

Classically, the phases of psycho-oncological interventions were of pre-diagnostic alarm (onset of symptoms and suspicion of the disease) and diagnosis phase (acute phase), the stage of processing (Grassi et al., 2005):

- **Pre-diagnosis phase:** is a key moment, represented by deep emotions and dramatic. The reaction is understandable alarm, marked by a sense of uncertainty and concern about the symptom. The general practitioner plays a key role in this step;
- **Diagnosis:** it overwhelms strikingly the person who suffers from the disease. It creates a range of emotions and behaviors. Within this condition, there are various reaction phases of the individual: shock, transition and disease processing;
- **Reordering phase:** When the patient lives with the disease and its consequences. He could search for new meanings attributed to the disease.

However, since current cancer conceptualization and management focuses on cancer issue as a chronic disease, psycho oncology seems to be fundamental also in supporting cancer survivors on the long-time. Research is demonstrating that adults diagnosed with cancer evidence generally positive psychosocial adjustment over time; however, there still is a risk for compromised psychological and physical health stemming from long-term or late effects of cancer and its treatment (Stanton et al., 2015).

According to the cognitive processing model of adjustment, recovering from a traumatic life event such as cancer requires either changing one's worldview so that it is congruent with the event, or changing one's understanding of the event in order to incorporate it into existing mental models. Both strategies require cognitive processing of the cancer experience. Dispositional qualities and cancer-related issues, however, may interfere with these cognitive processes and thereby contribute to cancer-related distress. Cancer-related distress may take the form of intrusive thoughts about the cancer, avoidance of reminders of the cancer, and hyperarousal (Eisenberg et al., 2015). This pattern of long-lasting worries and concerns about cancer was identified yet in 1981 in childhood as the “Damocles Syndrome” (Koocher & O’Malley, 1981).

## 2.1 Creating Wellbeing

Therefore, surviving cancer does not just mean recovering one's physical health and adding theoretical years back to one's life expectancy; it also means coping with emotional, social, occupational, financial issues that accompany the acute, and sometimes chronic, experience of cancer. Dealing with this, in order to restore subjective well-being has been defined as hygiology, "locating and developing personal and social resources and adaptive tendencies,"(Super, 1955) even in the midst of distressing or abnormal life conditions.

According to hygiology, health can be defined in relative terms; different individuals faced with cancer may differ markedly in their psychological adaptation based, in part, on the strengths, resources, and coping methods. Rather than focusing only on ameliorating psychological symptoms (anxiety, depression) , a hygiological response would be more concerned with how to support individuals' positive coping tendencies and resources (Lent, 2007). According to this perspective, areas that should be considered and assessed in cancer survivors are (Hoffman et al., 2013):

- *Problematic event and internal states:* in a cancer diagnosis, the threatening event is not only the diagnosis itself, but also the events regarding treatment and practical life impairments, along with the individual internal states depending from the idiographic reaction to these events;
- *Coping appraisal and strategies:* coping appraisal is the cognitive process people engage in when appraising a stressor (i.e. cancer diagnosis) and their own capability to deal with it; it is linked to internal characteristics, as the perceived threat, and to available resources such as financial, social support, and treatment access. Coping strategies are, instead, implemented to deal with stressor; they can be problem-focused, aimed to resolve the stressor, emotion-focused, aimed at managing internal aspects of the stressor and, in cancer, meaning-making, the recovery of meaning or making new meaning when facing highly stressful situations (Park, 2010);
- *Problem-related coping efficacy:* a form of self-efficacy that refers to people's beliefs in the ability to deal with this specific stressor (i.e. cancer). These beliefs can affect how people perceive and react to adverse life events;

- *Personality and affective dispositions:* stable traits that affect how people appraise life events. The most studied traits referring to cancer response are: dispositional optimism, positive and negative affect and general self-efficacy;
- *Environmental support and resources:* from emotional and cognitive support to practical resources;
- *Adjustment outcomes:* changes in psychological and role functioning and in emotional well-being and Quality of Life (QoL) after cancer diagnosis.

## 2.2 Symptomatology

Anxiety, depression, irritability and anger are common reactions in cancer patients and these behaviors are a normal response to this experience. However, when these states' levels are high or excessive anxiety, depression and anger become pathological, especially when these reactions are relatively independent from stimuli or situations, when interpersonal relationships and the ability to interact with others are disturbed and altered.

### 2.2.1 Psychopathological Risk

Literature has reached some evidences on the main psychopathological disease that could affect cancer patients, that could mainly onset at the moment of diagnosis or during the treatment:

- **Depression:** It is a very common disorder among these patients and is the most difficult to diagnose properly. Depression is accompanied by activation of the inflammatory response of the organism, which as well as being partly responsible for the peripheral neuropathy, thereby contributing to the pain experienced from cancer patients, causes a dysfunction of the immune system (Evans, 2005; Raison et al., 2006). Many of the physical symptoms of depression (alteration in body weight, insomnia, fatigue, malaise and suffering) may be confused with side effects of cancer treatment, such as chemotherapy, and so it is not always easy to diagnose it. The diagnosis is only possible through the symptoms of mental and emotional sphere: low mood, like crying, guilt, loss of interest and anhedonia (inability to experience pleasure), feeling of being a burden to others people and poor

concentration, agitation or retardation, irritability, social withdrawal and self-injurious thoughts or actions. Depression is the most important factor related to the deterioration in the Quality of Life of these patients (Somerset et al., 2004). It may put at risk the survival of the patient, increasing mortality and the risk of suicide. A study carried out in Denmark (Yousaf et al., 2005), shows that, compared to the general population the risk of suicide among patients with a diagnosis of cancer is higher than the 50% for men and 30% for women without consider the differences for the type of cancer and for the prognosis.

- **Anxiety:** It is a normal response to situations unknown, uncertain or dangerous. Many cancer patients experience anxiety in the initial period, at the stage of diagnosis. It could easily convert in a chronic state, triggered by additional uncertainties, such as waiting for the results of diagnostic tests for suspected recurrence (Barraclough, 2004).
- **Denial and repression:** Denial is a psychological mechanism used facing a traumatic threat. It is a denial that covers emotional, cognitive and behavioral range and tries to make the perceived threats tolerable and even easier to manage. There is talk of denial in those cancer patients who apparently underestimate the severity of the diagnosis and prognosis. While the adaptive denial minimizes the threat and danger, pathological denial involves a real break with reality. It could be the result of a split in the sense of reactive depression and / or vacuum experienced as intolerable (Razavi & Delvaux, 2002). Repression is different from denial because it minimizes or removes internal stimuli (needs and desires). Repression is a conscious mechanism of exclusion of certain feelings that would lead one to despair. Pathological repression and denial are both negative: "I am sick", "I'm fine" it is the expression of a neutralization of meaning, in the case of denial, or affection, in the case of repression (Razavi & Delvaux, 2002).
- **Suicide and self-harm:** Many cancer patients admit they thought about suicide. Epidemiological studies indicate that the rate of suicide among cancer patients is twice that of the general population, with the peak in the first year after diagnosis. Having the ability to choose to end their lives gives

them the impression of being in control of the future. The overdose of drugs is the method of suicide and self-harm typical of cancer patients. Other types of self-injurious behavior can be non-cooperation with the therapies, alcohol abuse or reckless driving (Barraclough, 2004).

### *2.2.2 Psychological symptomatology in survivors*

Many studies have been conducted in order to identify main psychological symptoms and psychopathological risk in cancer survivor population. In younger women with breast cancer, there is an evident tendency to feel depressed, irritable, tense, or worried (Arndt et al., 2004). In a national survey conducted in the US, emerged that cancer survivors reported significant poorer mental health and mood, along with poorer environmental mastery and self-acceptance (Costanzo et al., 2009). In an Internet based survey conducted on a population with different cancer site emerged that the emotional toll of cancer survivorship was substantial 72% of respondents state they had to deal with depression as a result of their cancer. Cancer survivorship issues remained long-term since 41% of survivors believed they would still die from cancer and 57% agreeing that cancer will always be a part of their life. These results are profound considering that the majority of responders were remote from their cancer diagnosis and direct treatment (Wolff, 2007). A 12 month study on women with breast cancer showed, at the diagnosis time, clinical relevant rates of depression (32.5% of the sample), anxiety (17.7 %) and mixed depression and anxiety (35%). Although anxious symptoms tend to decrease, depression seem to have a fluctuant trend. At the last evaluation, after a year, women with higher levels of morbidity were less likely to complete the study and it is possible that the most distressed and physically unwell patients were those who declined participation at all (Stafford et al., 2013). Still in women with breast cancer was possible to detect, after three years from diagnosis, a high risk to develop anxiety (38% of the sample), depression (22%) and post-traumatic stress disorder (12%) (Menhert & Koch, 2008). In a sample of man with prostate cancer, 16% of the sample revealed psychological distress and 6% psychopathological symptoms, especially in presence of a lack of social support and detrimental interactions (Menhert et al., 2009). However, the most commonly reported problem and one of the most prevalent areas of unmet need for cancer survivors is Fear of Cancer Recurrence (FCR) defined as “fear that cancer could return or progress in the same place or in another part of the body”

(Simard et al., 2010). In a large sample of cancer survivors, FCR remained active in 66% of the sample (Wolff, 2007). This symptom seems to be stable along the survivorship and highly related to young age, physical symptoms gravity, psychological distress and worst QoL (Simard et al., 2013).

### *2.2.3 In Ovarian cancer*

In Stafford et al. study, was investigated also a sample of Ovarian cancer survivors, who reported no differences than breast cancer (Stafford et al., 2013). A specific longitudinal investigation of psychological morbidity in patients with ovarian cancer showed that most of the women were “occasional” cases of anxiety (52%) and a subset of patients were stable cases of anxiety (22%), especially in younger women (Goncalves, 2008). A recent meta-analysis showed that over the trajectory of the Ovarian Cancer treatment journey, depression was highest before the initiation of treatment (25.3%) before dropping during treatment (23%) and decreasing again after the cessation of treatment (12.7%). In contrast, anxiety was lowest prior to treatment (19.1%) before rising sharply and then plateauing during and after the cessation of treatment (26.2% and 27.1%, respectively). All of this rates result significantly higher than healthy women range (Watts et al., 2015).

## **2.3 Coping and Quality of Life**

Coping strategies employed by individuals with cancer are fundamental in increasing or decreasing psychological distress, directly affecting patients’ Quality of Life (QoL).

The most frequent coping responses in cancer are (Cacace & Cantelmi, 2009):

- **Despair:** Characterized by high levels of anxiety and depression. The individual has no strategies for the diagnosis acceptance;
- **Anxious concern:** High levels of anxiety. For this individual cancer becomes central to his existence and to the behavioral level he may provide a continuous demand for visits or, on the contrary, attempts to escape from the context of care;

- **Stoic acceptance:** On an emotional level the subject has low levels of anxiety and depression. They think they have little control over events and on the disease. And they resigned to accept what fate has determined;
- **Denial with avoidance:** Low levels of anxiety and depression. The individual tends to avoid confrontation with the reality of the disease;
- **Fighting spirit:** This type of person has adequate levels of anxiety and depression compared to the situation, the perception of a partial control on the events and behavioral level has a greater adherence to treatment with a wider acceptance of the disease condition.

Literature shows that for individuals living with an illness such as advanced cancer, acceptance coping strategies means to invest in a renewed sense of self (Angiola & Bowen, 2013). As a coping strategy frequently used by individuals with advanced cancer in order to accept somehow their condition, studies detected spirituality and religion (Alcorn et al., 2010; Peteet & Balboni, 2013). This strategy correlate with an increase in QoL (Balboni et al., 2007) and to the attribution of meaning to illness condition (Carlson & Halifax, 2011). In a study conducted on a sample of cancer patients emerged that experiential avoidance appeared to be incompatible with valued living. Values in that study are conceptualized as qualities of ideal behavior, providing structure and coherence to life and guiding purposeful action; are pervasive across contexts and periods, and enable people to pursue what they care about most deeply in life. Greater success at valued living was generally correlated with less cancer-related distress, improved well-being, and less avoidant coping (Ciarrocchi et al., 2010).

### *2.3.1 In Ovarian Cancer*

In Ovarian Cancer, QoL is one of the most relevant outcomes mostly because advances in medicine developed new treatments, but these have associated side-effects and toxicities that may impact on women QoL. Therefore, when considering a treatment plan, risks and benefits must be balanced in order to achieve an optimal QoL (Goncalves, 2015). In a longitudinal study conducted on ovarian cancer patients has been demonstrated that an improvement in QoL, here observed as for global function, appetite loss and constipation, during the first 3 months of treatment is significantly

associated with improved survival time (Gupta et al., 2013). In a sample of women with recurrent ovarian cancer, progressive deterioration in QoL could be an indicator of death within six months and coping strategies based on acceptance could ameliorate perceived QoL (Price et al., 2013). QoL in women with Ovarian Cancer seems to be directly affected by surgical treatment (frequently leading to hysterectomy of oophorectomy), organic factors treatment related (pain, nausea, fatigue), psychological distress (anxiety, anger, guilt and depression) and sexual dysfunctions (Wenzel et al., 2003; Penson et al., 2006; Lowe et al., 2007). Other risk factors for a QoL deterioration in these patients are prolonged and multimodal treatments, young age and disengaged coping strategies (Pearman, 2003). Also in women with recurrent ovarian cancer, educating to acceptance thus reducing avoidance, seems to have a great healthy effect on Quality of Life (Rost et al., 2012).

#### **2.4 Support, intimacy and sexuality**

The perceived support, related to friends and to intimate relationship, seems to play key role in cancer adaptation and survival. In women with breast cancer has been shown that a perceived lack of friendship, marital and familial support correlate with higher distress and more difficulties in illness acceptance and management (Manne et al., 2003). Evidences have been collected that a lack of support reciprocity with one's partner often exacerbates coping difficulties in the context of a range of life-threatening illness in which both the patient and their partner face unique stressors. The nature of these unsupportive interactions suggest that one pattern involves avoidance of the patient or criticism of her coping efforts (Mallinckrodt et al., 2012). Also in male with prostate cancer collaborative coping, meant as spouses pooling resources and problem solving jointly, may be associated with better daily mood, with heightened perceptions of efficacy in coping with stressful events (Berg et al., 2008).

One aspect of the couple, which can be affected directly or indirectly from oncological disease and its treatment, is sexuality (Pugliese, 2011). The proposed therapies against cancer are often very aggressive, deeply affecting the patient physically, psychologically and socially. Many treatments alter the image that patients have of their body, such as mutilation, disfigurement and changes in physical functioning. It is possible that the patient feels less attractive and confident (Razavi, Delvaux and De Cock, 2002). In addition, the partner is the one who bears the brunt among the people

close to the patient, both emotionally and practically. It can happen that the healthy partner to avoid all sexual approach because of concern for the other. While patients who do not have a partner may not feel able to take on new relationships (Barraclough, 2004).

Issues for discussion and communication, expression and sharing emotions and consideration of each other's needs (Pugliese, 2011) are challenging the couple's relationship, already suffering from the disease. It is normal to lose interest in sexual activity immediately after diagnosis and during treatments, mainly because people are confronted with consequences such as anxiety, depression, pain and fatigue (Pugliese, 2011). Different cancer treatments can determine for example, enlargements of the breasts, hair loss, hot flashes and reduced energy levels, which are disrupting your body image, his manhood and, therefore, sexual desire (Pugliese, 2011) . In women as well as certain changes in body image always, certain therapies can cause menopause or fertility problems. In fact, an early menopause, the inability to have children, change body (like due to a mastectomy), the Radical Hysterectomy (that is, the total export of the uterus, the gonads and the upper third of the vagina), the psycho-physical stress, can lead to her not to be seen more as a desirable woman (Razavi, Delvaux and De Cock, 2002; Pugliese, 2011). The impact on fertility of patients depends on the sex, age and the therapies applied, as the type of chemotherapy or the doses of irradiation (Razavi, Delvaux and De Cock, 2002).

#### *2.4.1 In Ovarian Cancer*

In Ovarian Cancer patients, the role of support should be deeply inflect in its aspect linked to intimacy and sexuality. In an epidemiological study conducted on women with ovarian cancer emerged that marital status is associated with improved survival (Mahdi et al., 2013). In studies on women with ovarian cancer emerged that social support could play a protective role with respect to IL-6 elevations, distress and depressive symptoms, with a consequent strong influence on QoL (Costanzo et al., 2005; Lutgendorf et al., 2008). The feature that could be underneath this association could be the emotional disclosure to the partner: when effectively implemented through a Guided Disclosure Protocol, it is effective in reducing perceived stress and improving Quality of Life (Arden-Closen et al., 2013).

In women with Ovarian Cancer, changes in sexuality can directly affect couple relationship (as reviewed in Gilbert et al., 2011). In addition, treatment-related infertility or the possibility of infertility on young women have a negative impact on couple and intimacy (as reviewed in Penrose et al., 2013). Analyzing the aspect of sexuality, there is evidence that gynecological cancer has a negative impact on each of the four stages of feminine sexual response: sexual desire, excitement, orgasm and sexual resolution (Laganà et al., 2005). Surgical treatments on parts of body linked to womanhood and femininity alter body image, with physical and emotional trauma (Juraskova et al., 2003) and this led to the labeling of these treatments as “invisibles femininity assaults” (Butler et al., 1998). Thus in women with Ovarian Cancer can be detected disabling problems with diminished sexual functioning, body image, and sudden identity changes due to the loss of physical integrity, leading to distancing in intimate relationships (Sacerdoti et al., 2010).

These patients frequently manifest distress, feeling of loss and do not feel a woman anymore (Juraskova et al., 2003; Stead et al., 2007; Sekse et al., 2010). This has a strong impact on sexual self-schema (Andersen, 1997; Carpenter et al., 2009), cognitive generalizations about sexual aspects of oneself that are manifest in current experience, guide sexual behavior and influence the processing of sexually relevant information.

Thus becomes evident that the type and radicalism of surgical treatment for Ovarian Cancer can influence sexual function and play a significant role in QoL (Carter et al., 2013). Gynecological cancer survivors seem to experience a broad range of sexual concerns after diagnosis and treatment; common concerns in the physical dimension were dyspareunia, changes in the vagina, and decreased sexual activity. In the psychological dimension, common concerns were decreased libido, alterations in body image, and anxiety related to sexual performance. And in the social dimension, common concerns were difficulty maintaining previous sexual roles, emotional distancing from the partner, and perceived change in the partner's level of sexual interest (Abbot-Anderson & Kwekkeboom, 2012) Women with ovarian cancer are affected in terms of body image, sexual functioning, wifhood and motherhood and reproductive ability (Bal et al., 2013).

**PART TWO**

**THE STUDY**



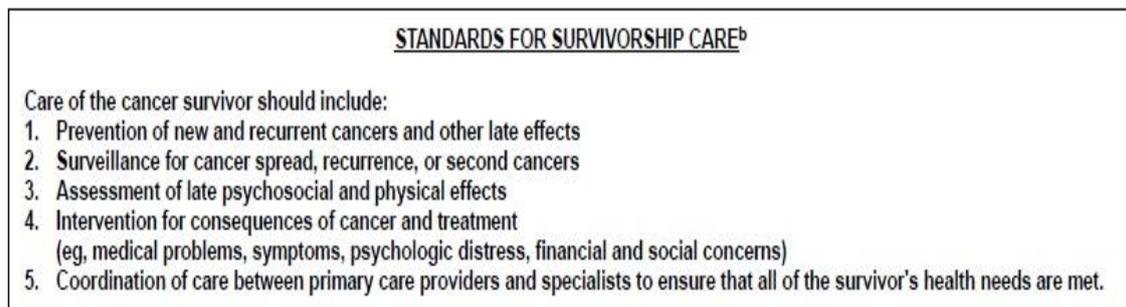
## INTRODUCTION AND RESEARCH RATIONALE

Actual scientific literature highlights how “the Great Connection” between mind and body in cancer is definitely a urgent topic.

Furthermore, current cancer conceptualization and management focuses on cancer issue as a chronic disease that could be directly modulated by psychosocial stressors (Karelina and DeVries, 2011).

In the National Comprehensive Cancer Network (NCCN) 2015 Guidelines “an individual is considered a cancer survivor from the time of diagnosis from the balance of his or her life.

Family members, friends and caregivers are also impacted. The vast and persistent impact [could be] on health, physical and mental states, health behaviors, professional and personal identity, sexuality and financial standings.” and it defines the standards of survivorship as follows (Fig.1):



**Fig. 1: Standards for Survivorship Care. From NCCN Practice Guidelines (2015)**

NCCN also focuses extensively on distress in cancer patients and on its management, defining the standards of care (Fig.2):

- Distress should be recognized, monitored, documented, and treated promptly at all stages of disease and in all settings.
- Screening should identify the level and nature of the distress.
- All patients should be screened for distress at their initial visit, at appropriate intervals, and as clinically indicated especially with changes in disease status (ie, remission, recurrence, progression, treatment-related complications).
- Distress should be assessed and managed according to clinical practice guidelines.
- Interdisciplinary institutional committees should be formed to implement standards for distress management.
- Educational and training programs should be developed to ensure that health care professionals and certified chaplains have knowledge and skills in the assessment and management of distress.
- Licensed mental health professionals and certified chaplains experienced in psychosocial aspects of cancer should be readily available as staff members or by referral.
- Medical care contracts should include reimbursement for services provided by mental health professionals.
- Clinical health outcomes measurement should include assessment of the psychosocial domain (eg, quality of life and patient and family satisfaction).
- Patients, families, and treatment teams should be informed that distress management is an integral part of total medical care and is provided with appropriate information about psychosocial services in the treatment center and the community.
- Quality of distress management programs/services should be included in institutional continuous quality improvement (CQI) projects.

**Fig. 2: Standards of Care for Distress Management. From NCCN Practice Guidelines (2015)**

Moreover, the wide impact that psychological features can have on cancer treatment, is also underlined by the international definition of the multidisciplinary team in cancer care, which officially collocates the psychologist/psychiatrist in the non-core team members (Fig.3):

Core team members	Non-core team members
<ul style="list-style-type: none"> <li>• Surgery</li> <li>• Medical oncology</li> <li>• Radiation oncology</li> <li>• Pathology</li> <li>• Radiology</li> <li>• Supportive care – oncology nurse/breast care nurse</li> <li>• General practice</li> </ul>	<ul style="list-style-type: none"> <li>• Genetic/hereditary counselling</li> <li>• Physiotherapy</li> <li>• Psychiatry/Psychology</li> <li>• Nuclear medicine</li> <li>• Plastic surgery</li> <li>• Palliative care</li> <li>• Social work</li> </ul>

**Fig. 3: Multidisciplinary care team membership for treatment planning. From <http://canceraustralia.gov.au>**

This led to the evidence of needing a holistic approach to cancer and cancer survivorship, as testified by the «Patient-centered cancer treatment planning: improving the quality of oncology care: Workshop summary» where is addressed the attention to the importance of comprehensive cancer care (Institute of Medicine's, 2011).

We chose to focus on Ovarian Cancer for different reasons. The nature of this cancer, which is an aggressive illness, associated with very poor survival and high recurrence rates. It is the fatal malignancy of the female genital tract and the fourth most common cause of female cancer death. This because it is detected at an advanced stage, with a 5-year survival rate of 46% for all the stages and 31% for advanced stages (Goncalves, 2010). The management of ovarian cancer that normally includes radical pelvic surgery and multiple aggressive courses of chemotherapy, worsen the impact of this illness on patients' Quality of Life.

Basing on literature, Ovarian Cancer patients and survivors tend to develop psychological disorders, as anxiety, depression and post-traumatic stress disorder (Hipkins et al., 2004; Norton et al., 2004; Gonçalves, 2008; Gonçalves, 2010; Gonçalves et al., 2011). There is also an evidence of occurrence of impairments in social, familial, vocational, physical and sexual functioning, not confined to diagnosis and treatment period but present also in short and long-term cancer survivors (Gonçalves, 2013).

In Italy, Ovarian Cancer is the 3% of cancer diagnosed to women and nearly one woman each 74 develops ovarian cancer (AIRTUM, 2014). Moreover, in Parma, the city where the study has been conducted, the incidence is of 46 new cases per year, (Fig.4):

<b>Parma Ovaio</b>		
	<b>Maschi</b>	<b>Femmine</b>
Numero di nuovi casi per anno (incidenza 2007–2011)	–	46
Proporzione sul totale dei tumori eccetto cute non melanoma (%)	–	3
Rischio di avere un tumore prima degli 85 anni (%)	–	1.5
Tasso standardizzato per età (E)	–	13.1
– Cambiamento annuale stimato negli ultimi 5 anni (%)	–	3.5[–5.2;13.1]
Numero di morti per anno (2007–2011)	–	34
Proporzione dei decessi oncologici (%)	–	5.1
Rischio di morire per la malattia prima degli 85 anni (%)	–	1.1
Tasso standardizzato (E)	–	8
– Cambiamento annuale stimato negli ultimi 5 anni (%)	–	–0.1[–11.7;13]
Sopravvivenza relativa (%) con [95% IC] (2000–2004) standardizzata per età		
1–anno	–	72[66–77]
5–anni	–	39[33–45]

**Fig .4: Epidemiology of Ovarian Cancer in Parma. Project ITACAN, AIRTUM (2015)**

Analyzing international literature on psychological features influencing illness adjustment emerged the fundamental aspect of social support (Cosentino & Pruneti, 2015). It is meant as the possibility to recognize and share the burden of a chronic and life-threatening disease as cancer with family, friends and significant ones. In Ovarian Cancer patients, literature highlights a withdrawal from intimate relationship, because of feelings of fear and shame patients can feel about their conditions. Also because of a strong maladaptive component linked to the sexual functioning and the body image that leads to a dramatic social retirement (Juraskova et al., 2003; Stead et al., 2007; Sekse et al., 2010 Sacerdoti et al., 2010).

In addition, coping strategies employed by individuals with cancer are fundamental in increasing or decreasing psychological distress, directly affecting patients' Quality of Life (QoL). For individuals living with an illness such as advanced cancer, acceptance coping strategies means to invest in a renewed sense of self (Angiola & Bowen, 2013). As a coping strategy frequently used by individuals with advanced cancer in order to accept somehow their condition, studies detected spirituality and religion (Alcorn et al., 2010; Peteet & Balboni, 2013). This strategy correlates with an improve in QoL (Balboni et al., 2007) and to the attribution of meaning to illness condition (Carlson & Halifax, 2011). In a study conducted on a sample of cancer patients emerged that experiential avoidance appeared to be incompatible with valued living. Values in that study are conceptualized as qualities of ideal behavior, providing structure and coherence to life and guiding purposeful action; are pervasive across contexts and periods, and enable people to pursue what they care about most deeply in life. Greater success at valued living was generally correlated with less cancer-related distress, improved well-being, and less avoidant coping (Ciarrocchi et al., 2010).

We also identified psychoneuroimmunological mechanisms that can play a protective role in cancer survivorship, identifying the importance of Heart Rate Variability (HRV) (Cosentino & Pruneti, 2015). HRV consists of the changes in the time intervals between consecutive heartbeats (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) and the balance between Sympathetic Nervous System (SNS) and Parasympathetic Nervous System (PNS) on Heart Rate determines it (Shaffer & Venner, 2013). In particular, the influence of PNS on HRV implements through the Vagus Nerve, which allows the physiological

mechanism of Respiratory Sinus Arrhythmia (RSA). The HR oscillations change in correspondence of breathing; they should be systematically increased during relaxed states and decreased in stress phases (Lehrer, 2013). We also found that through anatomical and functional specific systems (Myelinated Vagus) there is a strict connection between HRV and psychological adaptive features (Porges, 2007;2009).

Therefore, we looked to this works from a different angle, trying to theoretically integrate these two prosperous fields in a complex “positive” model of direct influence of specific psychological factors on quality of cancer survivorship. We tried to focus on how psychological and physiological features could interact in a protective way on cancer patient.

We stated this model “Integrated Model of Defense” (IMD, Fig.5.; Cosentino & Pruneti,2015) :

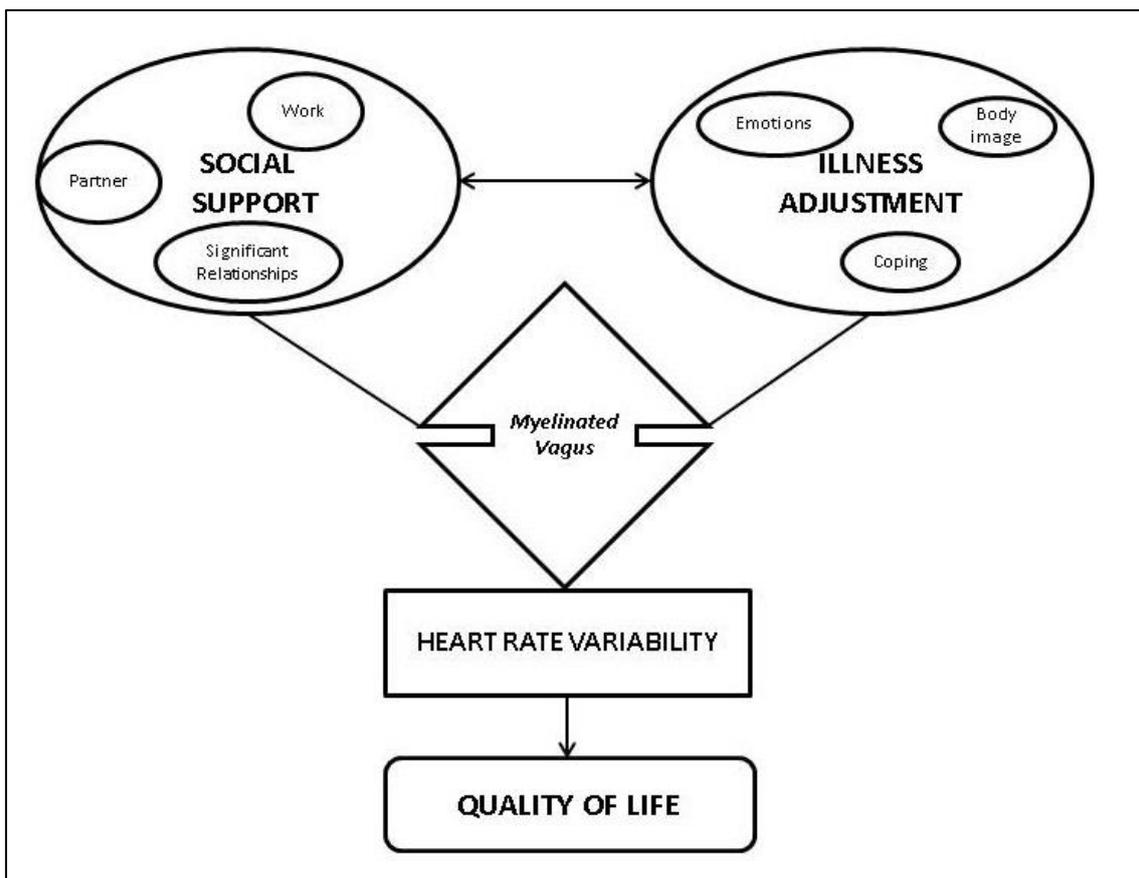


Fig. 5: Integrated Model of Defense (adapted from Cosentino & Pruneti, 2015)

We focused on the protective role that physiological activity (HRV) through anatomical and functional specific systems (Myelinated Vagus) could have in cancer survivorship. Nevertheless, referring to the latest neuroscientific theories and, in particular, on Porges' Polyvagal Theory, we noticed the possible relation between HRV and the psychological conditions of cancer patients, in particular the social support, meant as the possibility to recognize and share the emotional burden of a chronic and life-threatening disease as cancer. Conversely, frequently this illness goes with a withdrawal from intimate relationship, because of feelings of fear and shame patients can feel about their conditions. This can be particularly true for Ovarian Cancer, where, as clearly shown in literature, there is a strong impact on the sexual functioning and the body image. We suppose that a good psychological illness adjustment could influence HRV thus improving the Quality of Life, that is nowadays one of the first issues in chronic cancer care.

The first step we had to make to investigate the presence of this model, was to evaluate, for the first time for all we know in Italy, a sample of Ovarian Cancer survivors.

We wanted to understand the psychological adjustment of these women, basing on the main features identified in literature, aiming to add literature on this subject.

We also evaluated their physiological adjustment, measured through the HRV at rest. We needed to have basic information on the ANS activity and on the relaxation capability in these women.

We also decided to compare our population to normative data found in literature, in order to understand if Italian women, in particular in the psychological adjustment, mirror what has been found yet in literature.

The second step, is to understand how this psychological and physiological variables correlates in this women and if there are some specific connection that start to support the hypothesis of an IMD in Ovarian Cancer.

## CHAPTER III

### THE RESEARCH

To answer the research question we had, we planned an observational, transversal, descriptive study.

Since, for all we know, this is the first study set on the Italian population, it is an exploratory pilot study.

#### **Aims:**

The aims of this study were:

- I. To assess the illness psychological adjustment in terms of perceived social support, body image, affective adjustment, coping towards cancer and Quality of Life;
- II. To have a basal measure of Heart Rate Variability;
- III. To see whether higher levels of Heart Rate Variability are associated to a better psychological adjustment;
- IV. To see whether a worst body image perception and maladaptive coping strategies are associated to a poorer Quality of Life.

#### **Method:**

##### *Participants*

In this investigation, we enrolled women following a follow-up program for Ovarian Cancer at the Oncological Clinic, Gynecological ward, University Hospital of Parma, Italy.

##### *Inclusion Criteria:*

- Ovarian Cancer Diagnosis from at least 6 months;
- No surgeries from at least 2 months;
- Not under chemotherapeutic treatment at the moment of recruiting;

- Italian nationality;
- Aged from 18;
- Reading and signing the informed consent document.

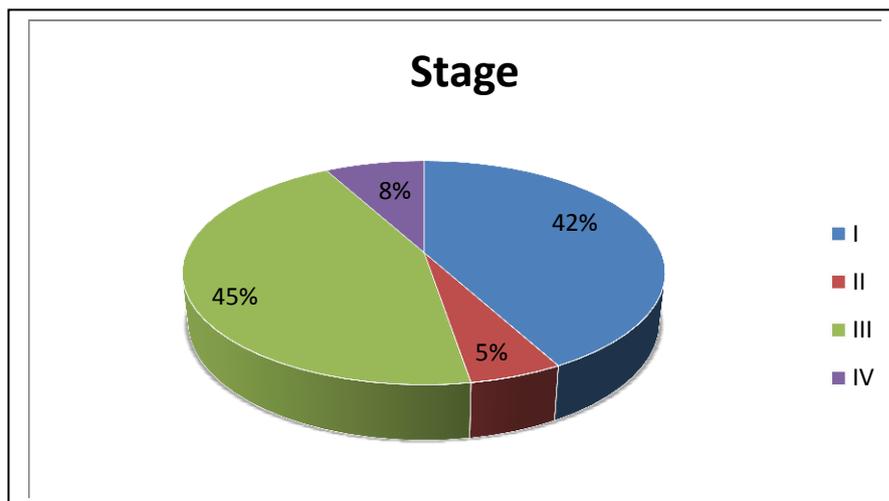
***Exclusion Criteria:***

- Positive anamnesis for previous psychiatric disorders;
- Under psychopharmacological treatment before the onset of cancer;
- Under pharmacological treatment with drugs directly affecting Heart Rate (i.e. beta- blockers).

The final sample consisted of 38 women aged from 29 to 80 years (M= 56,08; SD=12,76). Considering the cancer characteristics, the sample was quite heterogeneous as resumed in Tab.1 and Fig.6:

**Tab. 1: Sample Characteristics, Pathological Anamnesis. Time from the diagnosis and Chemotherapeutic treatment**

	<b>N</b>	<b>Min</b>	<b>Max</b>	<b>Mean</b>	<b>SD</b>
<b>Time</b>	38	1	10	2.39	1.8
<b>Diagnosis(y)</b>					
<b>Last</b>	25	1	70	16.80	17.8
<b>Chemo(m)</b>					
<b>N°Chemo</b>	25	3	7	5.96	.735
<b>cycles</b>					



**Fig. 6 : Cancer stage at the moment of the diagnosis, according to FIGO classification**

Of these women, the 73,7% had a partner (husband or companion), the 26,3% had not (widow, or divorced or single); the 55.3% had children before the onset of cancer while the 44.7% did not. Lastly, the 52,6 % had a high school diploma, the 23,7 % a secondary school diploma, the 13,2% a degree and 10,5% attended only the primary school.

### *Instruments*

Each participant was asked to fulfill a battery of test (see Appendix I) composed by:

- a) **Psycho-oncological record:** A sheet fulfilled by the examiner, to collect general information on the patient (name, age, work, education, social status, children), on the disease's course (type of cancer, stage, type of treatment, and actual cancer status), and on the presence of psychological/psychiatric/psychopharmacological support;
- b) **Multidimensional Scale of Perceived Social Support (MSPSS; Zimet,Dahlen, Zimet & Farley, 1998; Prezza & Principato, 2002):** is a brief self-report questionnaire designed to measure perceptions of support from 3 sources: Family, Friends, and a Significant Other. The scale is comprised of a

total of 12 items, with four items for each subscale. It is frequently used with people suffering from cancer (Hann et al., 2002; Karanci & Erkan, 2007; Bozo et al., 2009). The Italian translation, validated on 782 individuals, has a Chronbach's  $\alpha = 0.880$ ;

- c) **Derridford Appearance Scale-59 (DAS-59, Carr&Harris, 2000; Moss, Cogliandro et al., 2013):** is a 59 items self-report questionnaire designed to generate a comprehensive assessment of disruption to everyday living, difficulties with personal relations, lowering of self-esteem and emotional distress that are the responses of individuals to living with problems of appearance. The scale is appropriate for all appearance problems ranging from visible disfigurements and deformities to aesthetic problems of appearance that may be obvious only to the person concerned. It is intended for use by adults aged 16 years and over.

For first, it gathers relevant demographic information and identifies the aspect of appearance that is of greatest concern to the respondent. Then, 57 items assess relevant psychological distress and dysfunction and 2 items assess physical distress and physical dysfunction. Severity of distress is measured on a 5-point Likert and the introductory section and a 'Not Applicable' (N/A) response category for most items make the scale equally available to respondents who are not concerned about their appearance such as those in the general population.

As well as a full-scale score (F-S), the DAS59 gives five factorial sub-scale:

1. General Self-consciousness of appearance (GSC);
2. Social Self-consciousness of appearance (SSC);
3. Sexual and Bodily Self-consciousness of appearance (SBSC);
4. Negative Self-concept (NSC);
5. Facial Self-consciousness of appearance (FSC).

The DAS59 is psychometrically robust and has been standardized on a large sample of the clinical population of pre-operative plastic surgery patients and a large sample of the general population including respondents who are not concerned about their appearance (Harris et al.,2004). For the Italian translation (Moss et al.,2013) Cronbach's  $\alpha$  was calculated for the full-scale score and five

factorial sub-scale scores, and all were within an acceptable range (full scale (FS) – alpha = 0.94; general self-consciousness (GSC), alpha = 0.79; sexual and body self-consciousness (SBSC), alpha = 0.76; negative self-concept (NSC), alpha = 0.83; facial self-consciousness (FSC), alpha = 0.55; social self-consciousness (SSC), alpha = 0.92).

**d) Mental Adjustment to Cancer (MAC, 40 item; Watson et al., 1988; Grassi & Watson, 1992):** is a specific psychometric instrument to investigate, through

40 items on a 4-point Likert scale, the prevalent patterns of coping to cancer:

1. Fighting Spirit, the tendency to confront and actively face the illness;
2. Anxious Preoccupation, the tendency to experience the illness as an event source of marked anxiety and tension;
3. Fatalism, the tendency to have a resigned and fatalistic attitude towards the illness;
4. Hopelessness/Helplessness, the tendency to adopt a pessimistic attitude about the illness;
5. Avoidance, the tendency to avoid direct confrontation with illness-related issues.

In the Italian translation, all of the five sub-scales showed acceptable levels of reliability, with Cronbach's  $\alpha$  coefficients ranging from 0.55 to 0.87.

**e) EORTC Quality of Life Questionnaire LQ-30 Version 3.0 (EORTC-QLQ30; Study Group on Quality of Life, 1993):** is an integrated system for

assessing the health-related Quality of Life (QoL) of cancer patients. It is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

A high score for a functional scale represents a high level of functioning, a high score for the global health status / QoL represents a high QoL and a high score for a symptom scale / item represents a high level of symptomatology.

Functional scales are:

1. Physical Functioning;
2. Role Functioning;
3. Emotional Functioning;
4. Cognitive Functioning;
5. Social Functioning.

Symptoms scales and items are:

1. Fatigue;
2. Nausea and Vomiting;
3. Pain;
4. Dyspnea;
5. Insomnia;
6. Appetite Loss;
7. Constipation;
8. Diarrhea;
9. Financial difficulties.

For the multi-items scales, there is an acceptable reliability, with a Chronbach's  $\alpha$  that ranges from .54 to .89.

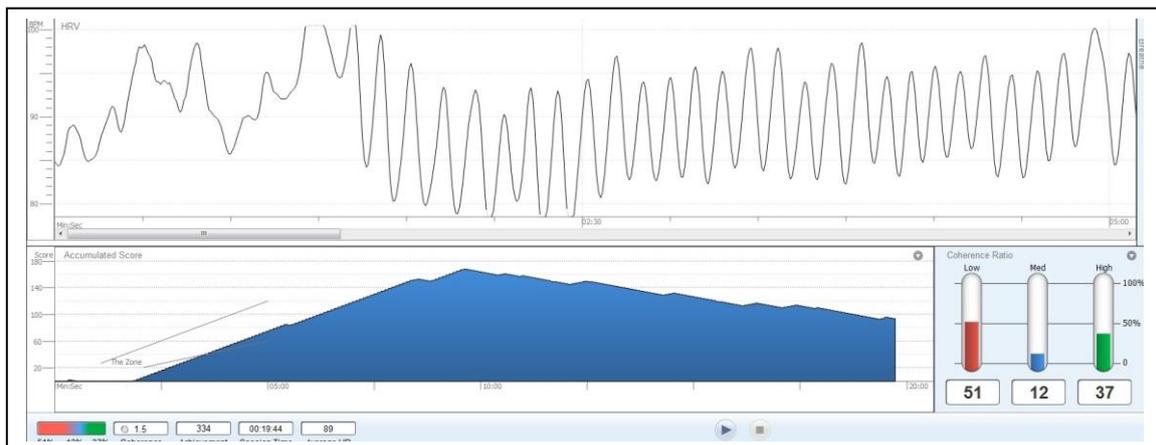
Moreover, for each participant, we recorded Short-Term Heart Rate Variability (5 minutes, Nunan et al., 2010) using:

- a) **emWavePro (HeartMath)**: is a recording and training system that objectively monitors heart rhythms and displays the physiological level of coherence between heart beat and respiration. Using a pulse sensor connected to the patient's earlobe and plugged into the Computer USB port (Fig.7):



**Fig. 7: Emwave Pro Sensor. From HeartMath UK**

It collects pulse data and translates coherence information into user-friendly graphics displayed on the computer screen (Fig.8):



**Fig. 8: Graphic displayed during the registration.**

**b) Kubios HRV 2.2 Software (Dpt of Applied Physics, University of Eastern Finland, Kuopio, Finland):** is a software that analyzes raw R-R Interval data registered through emWave, and gives back a sheet with Time-

Domain indexes, Frequency-Domain indexes and Non-Linear Results (see Appendix II).

### *Procedure*

We attended for 4 months the oncological follow-up ambulatory at the Gynecological ward of the Hospital of Parma.

We recruited from the daily register women with a diagnosis of ovarian cancer.

At the end of the routine follow-up visit, the gynecologist or surgeon on duty proposed each patient to participate to the study and sent her to the examiner in a private room. Once there, the examiner presented the study in detail, and gave to the patient the informed consent document.

After reading and signing the document, there was a brief clinical interview, in order to verify inclusion and exclusion criteria.

Immediately after the interview, the patient was asked to complete the battery of test (40 minutes approx.).

Once finished the battery, the patient was asked to stay still and as relaxed as possible, in order to record HRV at rest. After a few minutes of adaptation (2-3 minutes approx.), the Short-Term registration (5 minutes) started.

## CHAPTER IV

### RESULTS

#### *DESCRIPTION OF THE ITALIAN SAMPLE*

In this chapter, we report the results on ovarian cancer sample (OvCa) are reported, useful for the description of the Italian sample pattern in psychological adjustment and HRV.

We try to answer to the research aims I and II.

The analysis treated here, includes descriptive statistics, analysis of the variance looking for possible moderators and comparison within the group using tTest.

#### **4.1 Descriptive Statistics**

##### *Social support*

In Tab.2 are reported the descriptive statistics computed on Multidimensional Scale of Perceived Social Support (MSPSS):

**Tab. 2: MSPSS. Descriptive Statistics**

	N	Minimum	Maximum	Mean		Std. Deviation
	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic
MSPSStot	38	2.33	7.00	5.9381	.14102	.85781
Sig. Oth.	38	3.25	7.00	6.3851	.12578	.76511
Family	38	1.00	7.00	5.8851	.18824	1.14503
Friends	38	2.00	7.00	5.5662	.20138	1.22492
Valid N (listwise)	38					

According to Zimet’s indication, we used the scales scores descriptors ad a guide. As written in the manual: “Any mean scale score ranging from 1 to 2.9 could be considered low support; a score of 3 to 5 could be considered moderate support; a score from 5.1 to 7 could be considered high support” (Zimet, 1998). Our sample has a high rate of perceived general social support (Me= 5.93), in particular coming from the Significant Other (Me=6.38). The most critical area in social support is, instead, the support coming from friends (Me=5,56).

*Body Image*

In Ta.b 3 are reported the descriptive statistics computed on the Derridford Appearance Scale-59 (DAS-59):

**Tab. 3: DAS-59. Descriptive statistics.**

	N	Minimum	Maximum	Mean		Std. Deviation
	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic
DAS_FS	38	31	160	85.97	4.017	24.436
DAS_GSC	38	9	63	28.97	1.772	10.779
DAS_SSC	38	4	37	21.68	1.130	6.876
DAS_NSC	38	5	20	10.97	.558	3.395
DAS_SBSC	38	1	33	13.95	1.066	6.485
DAS_FSC	38	0	15	5.57	.570	3.468
DAS_Distress	38	0	8	3.16	.321	1.951
Valid N (listwise)	38					

FS,Full Score; GSC, general self-consciousness; SSC, social self-consciousness; NSC, negative self-consciousness; SBSC, sexual and bodily self-consciousness; FSC, facial self-consciousness.

Generally, the interpretation of these scales is “the higher,the worst”, hence, these women seem to have some general concerns about their appearance (Me=85.97, S.D.=24.4).

In order to better focus the characteristics of the sample, we compared them with the normative values of different populations given in the questionnaire’s manual (Carr et al.,2004) and, when possible and methodologically correct, we applied “tTest” to evaluate the presence of significant differences.

Respondents CONCERNED about their appearance							Respondents UNCONCERNED about their appearance						
WOMEN aged 31 - 60 years (N=189)							WOMEN aged 31 - 60 years (N=124)						
	F-S	GSC	SSC	NSC	SBSC	FSC		F-S	GSC	SSC	NSC	SBSC	FSC
Mean	82.3	32.9	16.1	12.5	14.0	2.7	Mean	22.1	3.8	2.9	1.6	10.4	0.6
SD	38.6	15.1	13.3	9.3	3.9	3.1	SD	16.7	5.4	6.6	3.2	3.6	1.3

Fig.9: DAS\_59 normative values. General population 30-61 CONCERNED/UNCONCERNED (Carr et al., 2004)

Tab.4: DAS-59: Mean and std.Dev in women with OvCa 30-61 (=26)

	F-S	GSC	SSC	NSC	SBSC	FSC
Mean	85.23	29.69	20.92	10.77	14.9	5.19
SD	22.6	11	6.4	2.6	6.6	3.3

Respondents CONCERNED about their appearance							Respondents UNCONCERNED about their appearance						
WOMEN aged 61 years and over (N=29)							WOMEN aged 61 years and over (N=64)						
	F-S	GSC	SSC	NSC	SBSC	FSC		F-S	GSC	SSC	NSC	SBSC	FSC
Mean	57.4	24.0	8.6	8.4	11.4	1.9	Mean	23.7	4.1	3.2	2.0	10.6	1.1
SD	23.6	11.0	8.6	7.5	3.7	2.5	SD	16.4	5.2	5.7	3.6	4.2	2.1

Fig. 10:DAS\_59 normative values. General population over 61 CONCERNED/UNCONCERNED (Carr et al., 2004)

Tab. 5: DAS-59. Mean and std. Dev in women with OvCa 61 years and more (=12)

	F-S	GSC	SSC	NSC	SBSC	FSC
Mean	87.73	27.27	23.45	11.45	13.36	6.45
SD	29.3	10.5	7.8	4.8	6.3	3.7

As shown in Tabs 4-5 and Fig. 9-10, the OvCa sample aged from 31 to 60, clearly gets a Full Score mean (Me=85.23) that is similar to the normative values in the CONCERNED general population. Moreover, also the other subscales have the same trend, with higher values of the OvCa sample in Social Self-Consciousness of Appearance, Sexual and Bodily self-consciousness of Appearance and Facial Self-Consciousness of appearance.

It is interesting to underline that, in our OvCa sample over 61, the pattern seems to worsen. In given normative data, the Full Score mean diminishes with age. In our sample it gets higher (Me=87.73), and it is clearly higher than the normative mean of the CONCERNED general population in each subscale (see tab.5 & fig.10).

We also compared our values with normative data drawn on a sample of women who had survived disease-free following treatment for carcinoma of the breast (Fig.11):

Respondents treated for unilateral carcinoma of the breast by LOCAL EXCISION OF THE TUMOUR AND RADIOTHERAPY (N=72) Age: Mean = 58.4 years, SD = 7.7							Respondents treated for unilateral carcinoma of the breast by MASTECTOMY (N=56) Age: mean= 59.6 years, SD=7.1						
	F-S	GSC	SSC	NSC	SBSC	FSC		F-S	GSC	SSC	NSC	SBSC	FSC
Mean	47.7	15.7	12.0	10.2	5.3	1.3	Mean	55.8	18.8	12.4	11.2	8.8	1.1
SD	29.1	14.8	8.5	3.9	5.0	1.6	SD	32.5	14.0	8.8	4.0	8.8	1.4

Fig. 11: DAS-59 normative values. Women with Breast Cancer with/without Mastectomy (Carr et al., 2004)

We found that DAS Full Score is significantly higher in OvCa sample compared both to women without mastectomy and with mastectomy (respectively  $t_{(110)} = -6.81; p < 0.000001$ ;  $t_{(94)} = -4.78; p < 0.000001$ ) and this pattern remains in almost each subscale (see Tab. 2 and Fig .3).

### *Coping Style*

In Tab. 6 are reported the descriptive statistics computed on the Mental Adjustment to Cancer (MAC):

**Tab.6: MAC. Descriptive statistics**

	N	Minimum	Maximum	Mean		Std. Deviation
	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic
MAC_f.s.	38	24.60	103.79	52.3619	3.07210	18.68688
MAC_h/h	38	6.00	21.03	10.4841	.62592	3.80730
MAC_a.p.	38	11.93	45.33	19.8076	1.16316	7.07521
MAC_f.	38	11.34	56.71	21.7892	1.71392	10.42538
MAC_a.	38	1	4	2.86	.186	1.134
Valid N (listwise)	38					

Fs, fighting spirit; h/h, hopelessness/helplessness; ap, anxious preoccupation; f, fatalism; a, avoidance.

We transformed the raw scores in Standardized Zpoints, except for the scale Avoidance(A) that is composed by a single item, in order to compare and classify the most used strategies. The most used strategy, as reported from OvCa sample, is Fighting Spirit (FS; Me=52.3), followed by Fatalism (F; Me=56.71). Strategies like Anxious Preoccupation (AP), Hopelessness/Helplessness (H/H) and A are less used.

### *Quality of Life*

In Tab. 8 are reported the descriptive statistics computed on the EORTC- Quality of Life Questionnaire 30 (EORTC-QLQ30) :

**Tab.8: EORTC-QLQ30. Descriptive Statistics**

	N	Minimum	Maximum	Mean		Std. Deviation
	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic
EORTC_QL2	38	17	100	66.32	3.070	18.674
PF2	38	20	100	79.08	3.177	19.327
RF2	38	0	100	73.43	5.055	30.750
EF	38	0	100	69.19	3.759	22.864
CF	38	50	100	81.03	2.324	14.137
SF	38	0	100	79.30	4.584	27.883
FA	38	0	100	40.78	4.984	30.319
NV	38	0	100	13.57	3.278	19.940
PA	38	0	100	30.65	5.062	30.788
DY	38	0	100	17.00	3.781	22.999
SL	38	0	100	38.65	5.716	34.766
AP	38	0	100	11.70	4.133	25.142
CO	38	0	100	20.70	5.385	32.758
DI	38	0	100	13.46	3.969	24.145
FI	38	0	100	12.59	4.159	25.300
Valid N (listwise)	38					

In this questionnaire, the interpretation of the scale is “the higher, the better” in the Global Quality of Life and Functional Scales (EORTC-QL2; PF2;RF2;EF;CF;SF;) while it is “the higher, the worse” for the remaining Symptoms Scales. The scores are presented in percentages.

Our sample has a rather good total Quality of Life (QL2 Me=66.32) with good levels of CF, SF and PF (respectively Me=81.03; Me=79.30; Me=79.08). The most critical functional area is the EF(Me=69.19).

Looking at the symptomatology, the ones referred as more present are FA (Me= 40.78) and SL(Me= 38.65), immediately followed by PA(Me=30.65).

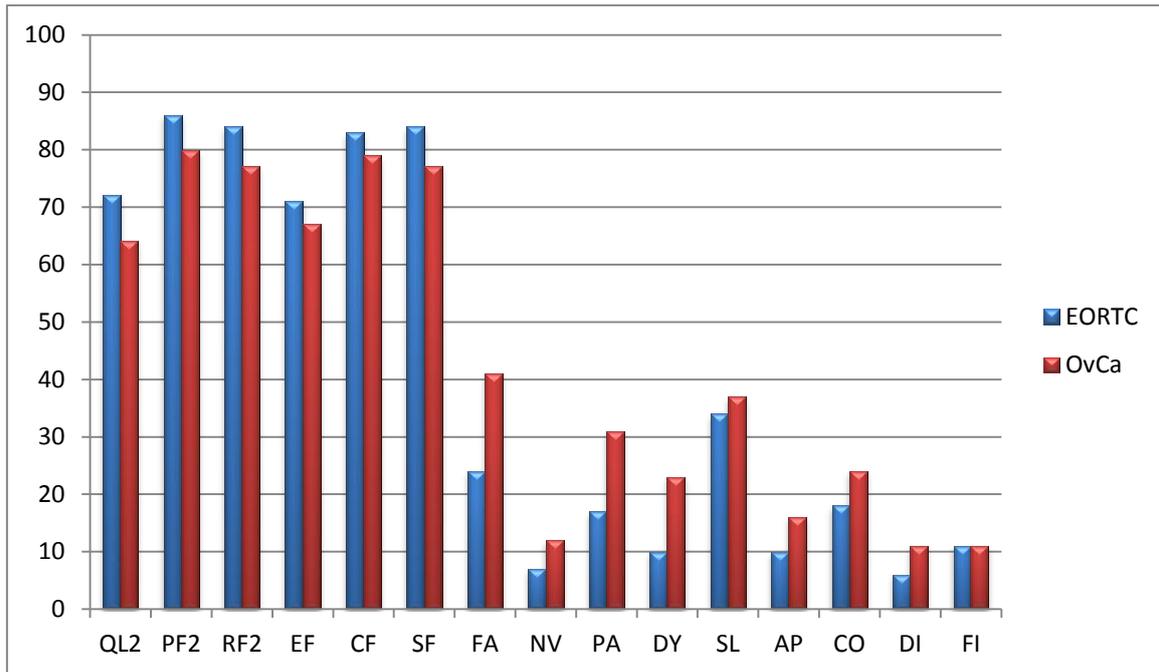
We compared our data, with the reference values given by EORTC (2008) for women affected by OvCa (Fig12):

<b>Gynaecological cancer (ovarian): all stages</b>			
<b>Constructed scales</b>		<b>Mean</b>	<b>(SD)</b>
Global health status/QoL	QL	60.0	(25.2)
Physical functioning	PF	77.5	(21.8)
Role Functioning	RF	66.0	(33.5)
Emotional functioning	EF	67.9	(25.3)
Cognitive functioning	CF	81.6	(22.4)
Social functioning	SF	72.1	(31.2)
Fatigue	FA	37.6	(28.8)
Nausea and vomiting	NV	11.2	(21.5)
Pain	PA	26.7	(28.7)
Dyspnoea	DY	19.4	(27.6)
Insomnia	SL	34.5	(33.7)
Appetite loss	AP	25.7	(34.2)
Constipation	CO	22.0	(30.6)
Diarrhoea	DI	10.8	(22.6)
Financial difficulties	FI	13.2	(26.1)

**Fig.12: EORTC Reference Values. All cancer stages**

Considering together the stages, our sample fits well the reference values, presenting slightly better values in QL and in the Functional Scales, except for SF. However, the sample presents slightly higher values also in the Symptoms scale, when compared to the reference values; hence our sample refers a wider presence of symptomatology.

We also analyzed the EORTC basing on the cancer stage, by splitting the sample in to early (1-2) and late (3-4) stages, as presented also in EORTC Manual (Fig. 13):



**Fig. 13: Graphic comparison between EORTC reference values and OvCa sample with 1-2 stages**

Comparing the early stages of pathology, we found that our sample has values decisively lower in each Functional Subscale and higher in each Symptom Scale, except for FI, which is similar for both the groups.

Comparing late stages of pathology (3-4) we found that our sample OvCa gets higher values than reference in almost each Function Scale and similar values in the Symptom Scales, excepting for SL, which is higher in OvCa sample (Fig.14):

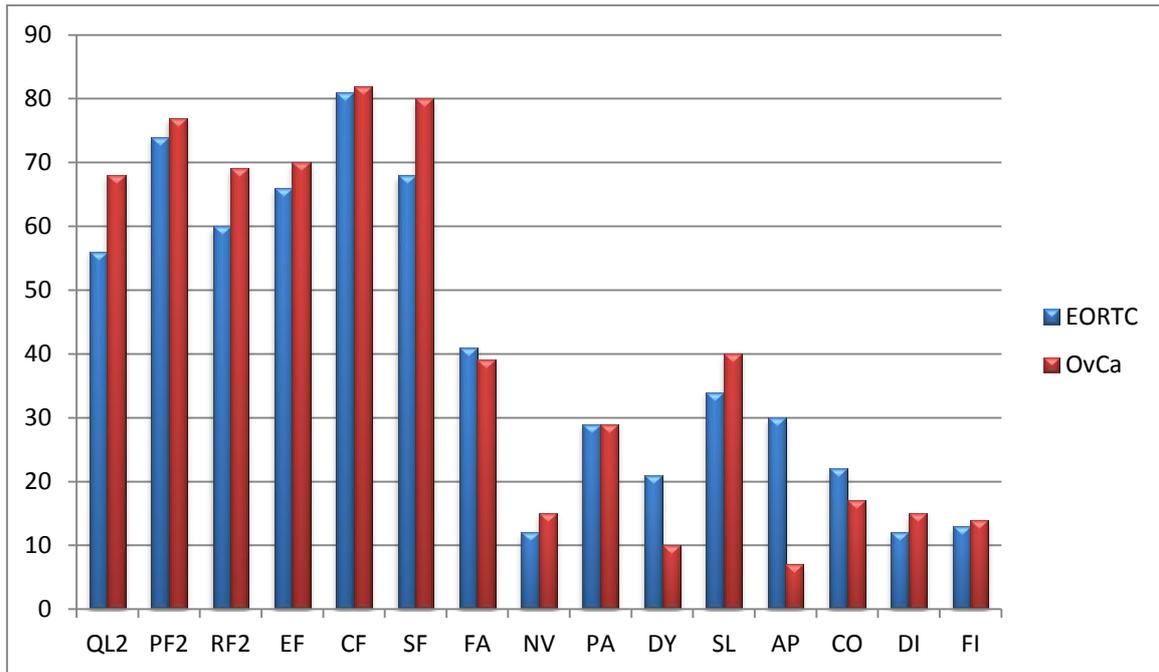


Fig. 14: Graphic comparison between EORTC reference values and OvCa sample with 3-4 stages

### Heart Rate Variability

In Tab. 9 are reported the descriptive statistics computed on the Heart Rate Variability (HRV):

Tab. 9: HRV. Descriptive statistics

	N	Maximum	Mean	Std. Deviation
	Statistic	Statistic	Statistic	Statistic
HRV_SDNNms	38	52,80	28,2132	9,89226
HRV_LF/HFms2	38	3,60	1,2321	,86136
Valid (listwise)	38			

SDNN, standard deviation of normal beat to beat interval; LF/HF, low frequencies high frequencies ratio.

The clinical interpretation of HRV parameters strictly depends on the measured function. Standard Deviation of NN intervals (SDNN) measured in ms, the time interval

between heartbeats. A higher SDNN reflects a higher HRV in general and a regular ANS function. Low Frequencies/High Frequencies Ratio (LF/HF), indicates overall balance between SNS and SNP. Higher values reflect SNS domination, while lower ones reflect PNS domination.

We compared our results with literature data on HRV SDNN in ovarian cancer patients, whose HRV was derived from patient's ECG obtained near diagnosis (De Couck & Gidron,2013).

Since their sample was composed by 58 women, we provide a "tTest" in order to verify the presence of significant differences. We found that our OvCa sample had a SDNN significantly higher than the other group ( $t_{(96)} = -3,67; p < 0,005$ ).

However, comparing OvCa HRV with those of healthy adults, using the large sample in Nunan et al., 2010, (SDNN Me=50; LF/HF Me=1.2) we found an evidently lower HRV SDNN in our OvCa sample (Me=28.2) and a similar value in LF/HF.

Taking inspiration from DeCouck's study, we also verify the percentage of OvCa sample with extremely low HRv, using the cut-off of SDNN < 20ms from previous studies (Mouton et al., 2012; DeCouck's & Gidron, 2013) and concluded that the 15,7% of the total sample had low HRV.

## **4.2 Analysis of the variance and comparison within group**

The normality of data distribution was tested computing skewness and kurtosis and then using the Kolmogorov-Smirnoff test. In case of not normal distribution, the data were transformed until skewness and kurtosis' level was adequately reduced. .

In order to verify the presence of possible categorical moderators, multivariate analysis of variance (MANOVA) and "t Test" were applied (Tab.10).

The assumption were controlled before applying the statistics and, in the case of MANOVA, the multivariate normality and homogeneity of covariate matrices were verified through Box test and Levene's test.

**Tab. 10: Comparison between categorical variables, questionnaires and HRV**

	MSPSS (MANOVA)	DAS-59 (tTest)	MAC (MANOVA)	EORTC- QLQ30 (MANOVA)	SDNN (tTest)	HRV
<b>Stage (1-2/3-4)</b>	n.s.	n.s.	n.s.	n.s.	n.s.	
<b>Comorbidity (yes/no)</b>	n.s.	n.s.	n.s.	n.s.	n.s.	
<b>Children (yes/no)</b>	n.s.	n.s.	n.s.	n.s.	n.s.	

Since no significant effects of these variables were found, the sample was split in two groups: reproductive age (< 51) vs non-reproductive age (>=51) at the moment of diagnosis. As is well known in the scientific literature (Gold et al., 2001; Progetto Menopausa Italia, 2005), 51 years is considered as a threshold for the menopause onset (Tab.11):

**Tab. 11: Comparison within group: age of diagnosis**

	MSPSS	DAS-59	MAC	EORTC- QLQ30	SDNN HRV
<b>Reproductive Age/Non reproductive</b>	n.s.	n.s.	n.s.	EF* FA* PA*	Sig* T(34)=-2.99 p<0,005

Women who were diagnosed with ovarian cancer in the reproductive age, seem have higher HRV (Me=32.9) than women not in reproductive age (Me= 23.930). This effect was controlled splitting the sample basing on the Median age (55 years) but no significant difference was found.

Moreover, using Pillai's trace, there was a significant effect of the age of diagnosis on the Emotional Functioning Scale,  $V = 0.28$ ,  $F(1, 35) = 2.5$ ,  $p < .05$ . There was also a significant effect of the age of diagnosis on Fatigue Symptoms,  $V = 0.28$ ,  $F(1, 35) = 2.5$ ,  $p < .0001$ . A significant effect of the age of diagnosis was also found on Pain Symptoms,  $V = 0.28$ ,  $F(1, 35) = 8.7$ ,  $p < .005$ .

### 4.3 Discussion

To summarize the results that have been obtained in this research on an Italian sample of women with ovarian cancer at the descriptive level, it is possible to say that:

- a) They report a high social support, in particular coming from the significant other and the family. The lowest are of social support is the one coming from friends;
- b) Their concerns on body appearance are similar to those of general population women concerned about their appearance. These concerns are higher than the ones reported by women with breast cancer with and without mastectomy. Women aged 61 and more seem to be more concerned than younger women and more than the general reference population;
- c) The most used coping strategies are Fighting Spirit, followed by Fatalism. Anxious Preoccupation, Hopelessness/Helplessness and Avoidance are less used;
- d) They report a global good level of Quality of Life. There is good functioning, whereas the most critical area of functioning is the Emotional one. Prevalent symptoms are Fatigue, Sleep Disturbances and Pain;
- e) They have SDNN Heart Rate Variability higher than the one reported by women with ovarian cancer at the moment of diagnosis, but nearly 50% lower than normative values in healthy population;
- f) A significant difference was found, within the sample, in HRV and Quality of Life, comparing women diagnosed in reproductive age with women diagnosed in non-reproductive age.

This investigation is, for all we know, the very first on an Italian sample of ovarian cancer survivors. We hope that these findings could enlighten weak points and strong points of these women, in order to push other researchers to investigate on this sample to come to a wider and generalizable comprehension of these features. We also hope to push clinicians to pay more attention to these psychological aspects, even if patients are not in a condition of manifest psychopathology.

This sample of Italian ovarian cancer survivors seemed to perceive a high support, in particular deriving from the “significant one” who, in this sample, is represented by the partner or the daughter. These women reported less support from friends, as data revealed, but they did not complain on this, actually they seemed active in keeping their friends far from the real concerns they were experiencing, in countertrended with existing literature (Ferrel et al., 2003). This particular pattern could be explained looking at the reference culture. In fact, it seems that in Italian culture, friends generally have a secondary place when it comes to share emotional serious concerns, that are more easily shared with the family, from which seems to come the higher valuable support.

Moving on body image, the women we assessed seemed to be highly concerned about their appearance. Our data revealed that these concerns affect in particular three areas: social life, sexual life and negative concept of their selves. These results mirror what a part of literature said yet (Juraskova et al., 2003; Sacerdoti et al., 2009) on the impact of ovarian cancer treatment on feminine identity, even if this aspect in this specific type of cancer is not widely investigated.

In scientific literature, considering the general population, age has minimal effects on body image (Cash & Henry, 1995). In our sample, instead, we saw that these concerns, in the younger women, were similar to those of the concerned general population but, surprisingly, were very higher in women older than 61. We hypothesized that this phenomenon could be due to a general process of appearance changing due to natural ageing to which adds the not normative loss of the reproductive organs, which are the origin of femininity. Thus, it could be possible that, in younger women, surviving cancer is motivational in increasing flexibility also in accepting changes in body image, thus reducing appearance concerns, even though younger women objectively have a wider loss in terms of fertility and changes due to premature menopause.

However, an interesting observation comes from the comparison with normative data coming from breast cancer survivors. Scientific literature (Fobair et al., 2006; Pelusi, 2006; Boquiren et al., 2015) widely analyzed the impact on body image in breast cancer, coming to evidence that is a central issue in illness adjustment. The

same interest is not currently applied to ovarian cancer, probably because the detrimental aesthetic effects of surgery are not as visible as for mastectomy. However, in our sample, we found that the concern is even higher than for breast cancer. It seemed reasonable to hypothesize that, in these women, the detrimental impact of cancer treatment on body image was strong, but it was not openly admitted, actually it was hidden, just like the physical (due to laparotomy) and identity (due to reproductive organs loss) scar.

The women we assessed, seemed to prefer coping strategies towards cancer, as Fighting Spirit and Fatalism. According to scientific literature, these strategies can be considered the more adaptive and functional for cancer adjustment (Classen et al., 1996; Cotton et al., 1999; Uchida & Akechi, 2015). Hence, these women report to be active and to accept their condition of cancer survivor with a good level of mental adjustment. However, we should underline that the Avoidance MAC scale, cannot be considered exhaustive, since it is composed by a single item. Even though the mean in this sample is quite low (Me= 2.86 on a maximum of 4) we cannot completely exclude a kind of cognitive denial to be present in this sample of survivors. Clinical observation pushes towards this question, since many of the assessed woman stated they just “tried to live as before cancer”, thus avoiding to consider themselves as cancer survivors.

Women we assessed seemed to have a good Quality of Life. They refer they could adequately resume their everyday life, even though with some limitations, in particular heavy physical activities, especially at home or at work. However, they report difficulties in emotional functioning, since they still feel somewhat depressed, nervous and angry. It is important to underline how the emotional distress, as evident in scientific literature, can contribute to the onset of symptoms like fatigue (Bower et al., 2000; NCCN, 2003; Weis & Horneber, 2015), sleep disturbance (Davidson et al., 2002; Nishiura et al., 2015) and pain (Koopman et al., 1998; Didwaniya et al., 2015). Thus, in these women we could hypothesize that a reduced emotional functioning, showed as the presence of recurrent thoughts, concerns and subclinical mood alterations, not always and properly shared with other significant

figures, as it was clinically observed, could cause the presence of a range of symptoms and surely have an impact on the general Quality of Life.

Moreover, comparing our sample to the reference values given in literature on ovarian cancer survivors, we found an interesting trend: women of our sample diagnosed with early stage cancer (1-2) seemed to have worst functioning and a higher number of symptomatology, compared to reference values; women diagnosed with late cancer stage (3-4) had better functioning and similar or lower symptomatology. To explain this result, we could hypothesize that, at least in our sample, receiving an advanced cancer diagnosis, with its high life threat, could drive these women to be more reactive in reconsidering their life. It seemed reasonable that having heavy treatments (surgery and chemotherapy) and thus deeply connecting with the “cancer environment” (other cancer patients, specific hospital structures, death of other cancer patients), could push them to fight for a better everyday life, thus understandably underestimating the presence of functional impairments or of specific symptomatology. Women diagnosed with early stage cancer, instead, who frequently have less aggressive treatments and familiarize less with the “cancer environment”, could be more overwhelmed from everyday life changes, thus reporting more impairment in functioning and more symptomatology, as they seem more resistant to changes in their life.

According to scientific literature, Heart Rate Variability can be definitely seen as an objective measure of emotional and social functioning both in healthy and ill population (McCraty et al., 1995; McCraty et al., 1998; Appelhans & Luecken, 2006; Francis et al., 2015).

In this sample, we found SDNN HRV to be higher than the one, present in literature, of women newly diagnosed with ovarian cancer (McCouck & Gidron, 2013). This can be easily explained through the fundamental difference of the assessment timing. Our women, being survivors, were far from the moment of diagnosis, so we could hypothesize that they familiarized with cancer and cancer effects, thus reducing the level of distress. However, coming to compare their SDNN HRV (Me=28.21 ms) to normative values of healthy people (Me=50 ms) we found a reduction in SDNN HRV of nearly 50 %. We should underline that, at the moment

of HRV assessment, these women were considered clinically healthy, so we could interpret this drastic reduction in terms of “residual distress”. Moreover, we should underline that in our sample LF/HF Ratio ( $Me=1,2ms^2$ ) is similar to the normative one ( $Me=1,2ms^2$ ). Then, we could hypothesize that, in these women, there is still a clinically significant impairment in sympathetic-vagal balance, due more to a decreased vagal tone (Kleiger et al., 1987) than to a condition of chronic sympathetic arousal (Saha et al., 2015). We could interpret this as a difficulty in relaxing and in detaching from recurring thoughts and concerns probably linked to cancer, along with a difficulty in sharing the emotive burden of these concerns with other people, thus creating a negative feedback loop that could foster physiological and emotional distress.

Lastly, it seems important to underline that, in our sample, the age of diagnosis had an important role in Quality of Life and HRV. In particular, we found that women diagnosed in reproductive age, had a higher SDNN HRV, higher Emotional Functioning and lower Fatigue and Pain than women diagnosed in non-reproductive age. This data seemed to contradict information coming from literature (Penrose et al., 2013). However, we have seen yet how this sample seem to behave in a particular way. In fact, as seen before for general Quality of Life and for body image, we could hypothesize that receiving a life threat diagnosis of cancer earlier in life, even though this diagnosis directly attack fertility, could push these women to react more than other women. In particular, we could say that, after treatment and in a condition of disease-free, women who were diagnosed earlier, had lower “residual distress” and reached a higher emotional functioning. Hence, we could suppose that, being diagnosed in reproductive age, could be a motivational push to fight against life difficulties. In fact, drastic changes that these woman had to bear, as the loss of fertility and premature menopause, could push them to admit more their concerns, thus accepting more their condition of cancer survivors, then reducing stress and amplifying emotional functioning.

## CHAPTER V

### RESULTS

#### *RESEARCHING PROOFS OF THE “GREAT CONNECTION”*

In this chapter are reported the results on our sample, useful for defining the relationship, in terms of association and/or possible causality, of the variables investigated.

We try to answer to the research aims III and IV.

The analysis treated here, includes correlations with p Pearson’s test and simple and multiple linear regression.

#### 5.1 Correlations

##### *a) Characteristics of the sample*

To evaluate possible correlations between our constructs, we applied point-biserial correlations in case of categorical variables and Pearson’s correlation for continuous variables.

Once tested for correlation categorical variables (early/advanced stage, children and comorbidity) significant correlations were found (Tab.12):

**Tab. 12: Correlation between age and HRV**

	<b>AGE</b>	<b>SDNN HRV</b>	<b>HF/LF HRV</b>
<b>AGE</b>	1	-.450**	-.385**
<b>SDNN HRV</b>	-.450**	1	n.s.
<b>HF/LF HRV</b>	-.385**	-.450**	1

There was a negative significant relationship between the age of these women and the SDNN HRV level,  $r = -.450$ ,  $p$  (one-tailed)  $< .05$  and also HL/LF HRV level,  $r = -.385$ ,  $p$ (one-tailed)  $< .05$ .

The coefficients of determination were, respectively  $R^2 = 0.2025$  for SDNN and  $R^2 = 0.1482$  for LF/HF. Therefore, we can state that age shares with SDNN the 20% of variability and it shares with LF/HF the 14% of variability.

**Tab.13: Significant correlation between age and EORTC-QLQ30 Functional Scales**

	<b>AGE</b>	<b>PF2</b>	<b>RF2</b>
<b>AGE</b>	1	-.370*	-.413**
<b>PF2</b>	-.370*	1	.652**
<b>RF2</b>	-.413**	.652**	1

There was a negative significant relationship between the age of these women and the Physical Function,  $r = -.370$ ,  $p$  (one-tailed)  $< .05$  and also Role Functioning,  $r = -.413$ ,  $p$ (one-tailed)  $< .001$ .

The coefficients of determination were, respectively  $R^2 = 0.1369$  for PF and  $R^2 = 0.1705$  for RF. Therefore, we can state that age shares with PF the 14% of variability and it shares with RF the 17% of variability (Tab. 13).

With the Symptom Scales, we found a significant relationship between age and Pain,  $r = .310$ ,  $p$  (one-tailed)  $p < .05$ ; the coefficient of determination  $R^2 = .0961$ , thus age shares with Pain the 9% of variability.

In DAS -59, there was a significant negative relationship between age and General Self-consciousness of appearance,  $r = -.352$ ,  $p$  (one-tailed)  $< .05$ , with  $R^2 = 0.1239$ , so the constructs share the 12% of variability.

**Tab. 14: Significant correlation between age and MSPSS**

	<b>AGE</b>	<b>MSPSS total</b>	<b>Friends</b>
<b>AGE</b>	1	-.276*	.280*
<b>MSPSS total</b>	-.276*	1	n.s.
<b>Friends</b>	.280*	n.s.	1

There was a negative significant relationship between age and total perceived support  $r = -.276$   $p$  (one-tailed) $<.05$  and Friends,  $r = .280$   $p$ (one-tailed) $<.001$ . The coefficient of determination were, respectively  $R^2=.076$  and  $R^2=.078$ , thus age shares the 7% of variability with the total perceived support and the 8% of variability with perceived support coming from friends (Tab. 14).

There were not significant relationship between age and MAC.

*b) Correlation between questionnaires*

**Tab. 15: Significant correlations between DAS-59 and EORTC-QLQ30 Function Scales**

	<b>QL2</b>	<b>PF2</b>	<b>EF</b>	<b>CF</b>	<b>DAS FS</b>	<b>DAS GSC</b>	<b>DAS NSC</b>
<b>QL2</b>	1	**	**	**	-.327*		-.452**
<b>PF2</b>	**	1	**	**	n.s.	n.s.	-.3331*
<b>EF</b>	**	**	1	**	n.s.	n.s.	-.401*
<b>CF</b>	**	**	**	1	-.356*	-.363*	-.480**
<b>DAS FS</b>	-.327*	n.s.	n.s.	-.356*	1	**	**
<b>DAS GSC</b>	n.s.	n.s.	n.s.	-.363*	**	1	**
<b>DAS NSC</b>	-.452**	-.3331*	-.401*	-.480**	**	**	1

There was a significant relationship between (Tab. 15):

- ✓ General Quality of Life and DAS-Full Score  $r = -.327$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1069$  and 10% of shared variance;
- ✓ General Quality of Life and Negative Self- Consciousness  $r = -.452$ ,  $p(\text{two-tailed}) < .001$ , with  $R^2 = .2043$  and 20% of shared variance;
- ✓ Physical Functioning and Negative Self- Consciousness  $r = -.331$ ,  $p(\text{two-tailed}) < .05$ , with  $R^2 = .1095$  and 11% of shared variance;
- ✓ Emotional Functioning and Negative Self- Consciousness  $r = -.401$ ,  $p(\text{two-tailed}) < .05$ , with  $R^2 = .1680$  and 17% of shared variance;
- ✓ Cognitive Functioning and Das Full Score  $r = -.356$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1267$  and 12% of shared variance;
- ✓ Cognitive Functioning and General Self- Consciousness  $r = -.363$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1317$  and 13% of shared variance;
- ✓ Cognitive Functioning and Negative Self- Consciousness  $r = -.480$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .2304$  and 23% of shared variance.

Considering the correlations between Quality of Life Functioning scales (EORTC-QLQ) and perceived social support (MSPSS) there was a significant relationship between:

- ✓ Role Functioning and Significant Other,  $r = .554$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .3069$  and 30% of shared variance;
- ✓ Emotional Functioning and Significant Other,  $r = .542$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .2937$  and 29% of shared variance;
- ✓ Cognitive Functioning and total Perceived Support,  $r = .411$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1689$  and 17% of shared variance;
- ✓ Cognitive Functioning and Significant Other,  $r = .473$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .2237$  and 22% of shared variance;
- ✓ Cognitive Functioning and Family,  $r = .418$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1747$  and 17% of shared variance.

**Tab. 16: Significant correlations between EORTC-QLQ30 and MAC**

	<b>QL2</b>	<b>PF2</b>	<b>RF2</b>	<b>EF</b>	<b>MAC_fat</b>	<b>MAC_a</b>
<b>QL2</b>	1	**	**	**	.364*	n.s.
<b>PF2</b>	**	1	**	**	.474**	n.s.
<b>RF2</b>	**	**	1	**	.475**	n.s.
<b>EF</b>	**	**	**	1	.495**	-.352*
<b>MAC_fat</b>	.364*	.474**	.475**	.495**	1	**
<b>MAC_a</b>	n.s.	n.s.	n.s.	-.352*	**	1

We found significant relationship between (Tab.16):

- ✓ General Quality of Life and Fatalism,  $r = .364$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1324$  and 13% of shared variance;
- ✓ Physical Functioning and Fatalism,  $r = .474$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .2246$  and 22% of shared variance;
- ✓ Role Functioning and Fatalism,  $r = .475$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .2256$  and 22% of shared variance;
- ✓ Emotional Functioning and Fatalism,  $r = .495$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .2450$  and 24% of shared variance;
- ✓ Emotional Functioning and Avoidance,  $r = -.352$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .21239$  and 12% of shared variance.

Considering the correlations between Coping style (MAC) and body image (DAS-59), we found significant relationship between:

- ✓ Helplessness/Hopelessness and DAS Full Score,  $r = .500$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .25$  and 25% of shared variance;
- ✓ Helplessness/Hopelessness and General Self-Consciousness,  $r = .380$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1444$  and 14% of shared variance;
- ✓ Helplessness/Hopelessness and Social Self-Consciousness,  $r = .433$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .1874$  and 19% of shared variance;
- ✓ Helplessness/Hopelessness and Negative Self-Consciousness,  $r = .426$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .1814$  and 18% of shared variance;

- ✓ Helplessness/Hopelessness and Sexual and Bodily Self-Consciousness,  $r = .397$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1576$  and 16% of shared variance;
- ✓ Anxious preoccupation and Sexual and Bodily Self-Consciousness,  $r = -.344$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1183$  and 12% of shared variance;
- ✓ Fatalism and Negative Self-Consciousness,  $r = -.513$   $p(\text{two-tailed}) < .001$ , with  $R^2 = .2631$  and 26% of shared variance.

**Tab. 17: Correlations between MAC and MSPSS**

	<b>MAC_fs</b>	<b>MAC_fat</b>	<b>MSPSS_Sig. Oth</b>	<b>MSPSS_Friends</b>
<b>MAC_fs</b>	1	-.337*	n.s.	-.342*
<b>MAC_fat</b>	-.337*	1	.360*	n.s.
<b>MSPSS_Sig.Oth.</b>	n.s.	.360*	1	**
<b>MSPSS_Friends</b>	-.342*	n.s.	**	1

We found significant relationships between (Tab.17):

- ✓ Fighting Spirit and Fatalism,  $r = -.337$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1135$  and 11% of shared variance;
- ✓ Fighting Spirit and perceived support from friends,  $r = -.342$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1169$  and 12% of shared variance;
- ✓ Fatalism and perceived support from the significant other,  $r = .360$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1296$  and 13% of shared variance.

**Tab. 18: Significant correlations between DAS-59 and MSPSS.**

	<b>DAS_SSC</b>	<b>DAS_NSC</b>	<b>MSPSS_Family</b>	<b>MSPSS_Friends</b>
<b>DAS_SSC</b>	1	n.s.	n.s.	.384*
<b>DAS_NSC</b>	n.s.	1	-.360*	n.s.
<b>MSPSS_Family</b>	n.s.	-.367*	1	-.360*
<b>MSPSS_Friends</b>	.384*	n.s.	-.360*	1

We found significant relationships between (Tab.18):

- ✓ Perceived support from friends and perceived support from family,  $r = -.360$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1296$  and 13% of shared variance;
- ✓ Social Self-Consciousness and Perceived friends' support,  $r = .384$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1474$  and 15% of shared variance;
- ✓ Negative Self Consciousness and perceived family's support,  $r = -.360$   $p(\text{two-tailed}) < .05$ , with  $R^2 = .1296$  and 13% of shared variance.

*c) Correlation between questionnaires and SDNN HRV*

There was no significant correlation between Body image, Coping strategy and Heart Rate Variability.

There was a significant relationship between perceived support from the significant other and HRV SDNN,  $r = .339$   $p(\text{one-tailed}) < .05$ , with  $R^2 = .1139$  and 11% of shared variance.

There was also a significant correlation between EORTC Role Functioning Scale and SDNN HRV,  $r = .479$   $p(\text{one-tailed}) < .001$ , with  $R^2 = .2294$  and 23% of shared variance.

## **5.2 Simple and multiple regression**

In order to verify the possible causal connection between the considered variables, after verifying for the assumptions, simple and multiple regression were applied to test the goodness of the theoretical model.

*a) HRV*

The first outcome considered for regression was HRV SDNN.

A simple regression was performed using as predictor MSPSS "significant other",  $F(1,33) = 4.27$   $p < .05$ . From this regression, emerges that the 11.5% of the HRV variation can be explained from the perceived support from the significant other.

A successive simple regression was performed using as predictor EORTC-QLQ30 “role functioning”,  $F(1,33)=9.810$   $p<.001$ . From this result, emerges that the 22.9% of the HRV variance can be explained from this variable.

Then a multiple Regression stepwise, with MSPSS (subscales), DAS-59 (subscales) and MAC (subscales) as predictors, was made (Tab.19):

**Tab. 19: Multiple stepwise regression MSPSS, DAS-59 and MAC by HRV**

	<b>B</b>	<b>(SE)B</b>	<b>β</b>
<b>Step1</b>			
<b>Constant</b>	<b>1.582</b>	<b>.107</b>	
<b>MSPSS Friends</b>	<b>-.592</b>	<b>.271</b>	<b>-.347*</b>
<b>Step2</b>			
<b>Constant</b>	<b>1.191</b>	<b>.200</b>	
<b>MSPSS Friends</b>	<b>-.696</b>	<b>.260</b>	<b>-.407*</b>
<b>DAS_FS</b>	<b>.005</b>	<b>.002</b>	<b>.344*</b>
<b>Step 3</b>			
<b>Constant</b>	<b>1.681</b>	<b>.256</b>	
<b>MSPSS Friends</b>	<b>-.743</b>	<b>.239</b>	<b>-.435**</b>
<b>DAS_FS</b>	<b>.007</b>	<b>.002</b>	<b>.453**</b>
<b>MAC_a</b>	<b>-.368</b>	<b>.134</b>	<b>-.391*</b>

*Note:  $R^2= .12$  for Step 1,  $\Delta R^2=.11$  for Step2,  $\Delta R^2=.14$  ( $p<.001$ ). \* $p<.05$ , \*\* $p<.001$*

This model of multiple regression shows that SDNN HRV is influenced by social support, body image and coping strategy. Totally, these predictors explain the 38% of HRV variance.

In particular, one of the most influent is general the general approach to appearance and body image ( $\beta=.453$ ), followed by support perceived from friends ( $\beta= -.435$ ) and the use of avoidance as coping strategy ( $\beta=-.391$ ).

b) *Quality of Life*

The global Quality of Life scale (QL2), was considered as second outcome.

A simple regression was performed using as predictor DAS\_Full Score,  $F(1,35)= 4.18$   $p<.05$ . From this regression, emerges that the 10,7% of Global Quality of Life variation is explained by the perception of body appearance ( $\beta= -.327$ ).

A stepwise multiple regression using as predictors MSPSS (subscales), DAS-59 (subscales) and MAC(subscales) was performed (Tab.20):

**Tab. 20: Multiple stepwise regression MSPSS, DAS-59 and MAC by EORTC QL2**

	<b>B</b>	<b>(SE)B</b>	<b><math>\beta</math></b>
<b>Costant</b>	45.53	9.45	
<b>MAC_fat</b>	392.49	169.9	.364*

*Note:  $R^2=.132$  ( $p<.05$ ). \* $p<.05$*

The stepwise regression excluded from the model variables regarding perceived social support and body image, keeping only the Fatalism Coping strategy.

The use of Fatalism, explains the 13.2% of global Quality of Life.

A multiple regression was also performed on the subsample who was diagnosed in reproductive age (under 51 years).

In this stepwise regression, the effects on global Quality of Life (QL2) of the predictors MSPSS (subscales), DAS-59 (subscales) and MAC(subscales) were evaluated (Tab.21):

**Tab. 21: Multiple stepwise regression MSPSS, DAS-59 and MAC by EORTC- QL2**

	<b>B</b>	<b>(SE)B</b>	<b><math>\beta</math></b>
<b>Costant</b>	111	19	
<b>DAS_FS</b>	-.999	.383	-1.09*
<b>DAS_SBSC</b>	3.02	1.11	.934*

*Note:  $R^2=.403$  ( $p<.05$ ). \* $p<.05$*

The regression excluded MSPSS and MAC, considering for the regression two scales of DAS-59.

The results of this regression shows that, the global Quality of Life is influenced by the perception of body appearance, and it explains the 40.3% of its variation.

Finally, also the Scale Emotional Functioning was taken as outcome in the whole sample and a multiple regression using as predictors MSPSS (subscales), DAS-59 (subscales) and MAC (subscales) was performed (Tab.22):

**Tab. 22: Multiple stepwise regression MSPSS, DAS-59 and MAC by EORTC EF**

	<b>B</b>	<b>(SE)B</b>	<b>β</b>
<b>Step1</b>			
<b>Constant</b>	<b>33.404</b>	<b>9.91</b>	
<b>MSPSS Sig. Oth.</b>	<b>49.606</b>	<b>13</b>	<b>.542**</b>
<b>Step2</b>			
<b>Constant</b>	<b>17.45</b>	<b>11.3</b>	
<b>MSPSS Sig. Oth</b>	<b>38.23</b>	<b>13</b>	<b>.418**</b>
<b>MAC_ Fat</b>	<b>456</b>	<b>188.5</b>	<b>.345*</b>

*Note: R<sup>2</sup>= .29 for Step 1, ΔR<sup>2</sup>=.10 for Step2 (p<.05). \*p<.05, \*\*p<.001*

The stepwise regression excluded from the model variables regarding body image, keeping as predictor perceived support from the significant other and the coping strategy “fatalism”. Totally, these predictors explain the 39% of Emotional Functioning.

In particular, one of the most influent is the support perceived from the significant other (β=.418), followed by the coping strategy “fatalism” (β= .345).

### 5.3 Discussion

The aims of this analysis were to see whether higher levels of Heart Rate Variability balance (coherence) are or not associated to a better psychological adjustment. Furthermore, we wanted to see whether a worst body image perception and maladaptive coping strategies are associated to a poorer Quality of Life.

Results that emerged from this sample of ovarian cancer survivors, seemed to confirm the presence of an integrated model of physiological and psychological adjustment, that could have a strong impact on the overall Quality of Life and, ultimately, on survivorship, here meant as a valuable surviving from the time of diagnosis.

First, we looked for the presence of significant relationships between proposed variables.

We found a preliminary significant relationship between aging and lower SDNN HRV values, which confirmed data coming from scientific literature on a loss of Vagal tone and a depressed HRV related to aging (Reardon & Malik, 1996; De Meersman & Stein, 2007). A significant relationship occurred also between aging and reduced Physical and Role functioning, along with an increase of pain symptomatology. We could hypothesize that this relationship mirrored the general lack of wellbeing caused by aging, both in reducing physical and role functioning, and amplifying pain symptomatology that, in this case, could be not neoplastic but linked to a general condition.

Aging had a significant relationship also with the body image domain, with the reduction of the general self-consciousness of appearance, that could be linked to a general reduction of the importance given to body image linked to aging (Tiggeman & Lynch, 2001; Tiggeman, 2004). Aging seems to be also related to a reduced perception of social support, along with a higher support received from friends. We could interpret this result as a double typical condition of aging. On one side, the higher perception of loneliness and not adequate support, as widely shown in scientific research (Hawkey & Cacioppo, 2007; Cacioppo et al., 2010) on the other side, the tendency on being more

sociable toward not familiar people, thus being more ready in sharing own personal experience with friends.

Until here, then, the relationship between psychological and physiological features and aging, seems to perfectly align with data coming from literature on normative aging.

Looking through the relationships present in our sample between the psychological variables, we could make some interesting observations. For first, results showed a strong relationship between body image and Quality of Life. These data suggest that higher concerns on body image, in particular the negative self-concept linked to appearance, were linked to a worst functioning in everyday life. The relation between the negative self-concept and a reduction in emotional functioning is understandable in terms of possible distress deriving from the perception of body appearance, as documented in literature (Carver et al. 1998). In addition, the relationship between negative concept and physical functioning could be interpreted as the effect of physical functionality reduction on the wider concept of appearance. Surprisingly, cognitive functioning seems to be strictly linked to body image. Since this relation is not well investigated in literature at the moment, it could be possible to hypothesize that a worst perception of one's own appearance, in these women, could incite negligence towards themselves, and thus, also a cognitive decline.

Moving to the relationship between social support and Quality of Life, we could confirm also in this sample, evidence coming from literature: the strong relationship between a high perceived social support and a better functioning in everyday life (Courtens et al., 1996; Parker et al., 2003; Westby et al., 2015).

Another interesting association is the one between fatalism as prevalent coping strategy and general functioning. In this sample fatalism, and not fighting spirit, was associated with a better physical, role and emotional functioning, thus according with a smaller part of scientific research that traced the same effect of this coping strategy (Cotton et al., 1999). In our sample, higher avoidance had an association with reduced emotional functioning, mirroring data coming from scientific research (Rost et al., 2012).

Another stimulating association was found between coping strategies and body image.

Helplessness/hopelessness approach to cancer was strictly linked to a worst body image perception in nearly each aspect. Moreover, anxious preoccupation was highly associated to a worst sexual self-perception, and we could hypothesize that a continuous preoccupation linked to cancer relapse, could be cause of a retirement from sexual intimacy, also considering this specific type of cancer. Our data, again suggested the importance of fatalism as coping strategy, since there was a negative association between this strategy and negative self-consciousness.

One more interesting associations was found between coping strategies and social support. From these results, we could hypothesize that the coping strategy fighting spirit was associated with a lower friends support, probably through the perception of more independence and self-determination. We could also suggest that fatalism, as a coping strategy, was associated with a higher perception of support from the significant one, maybe because, through this coping strategy, there was a higher rate of appreciation also towards a significant figure. We underline, at last, the negative relationship between fatalism and fighting spirit in our sample. This could suggest that fatalism is nearer to acceptance than fighting spirit, that could represent, in this sample, just an outward “fighting” approach to cancer.

The relationship between a higher perception of support from the family and a reduced negative self-consciousness, let us hypothesize that the family support could have a “buffer effect” on the acceptance of one’s own body image. The negative association between support from friends and social self-consciousness suggested that, in these women, the contact with friends could cause a greater difficulty in accepting the appearance, thus leading to a worst social consciousness of body image.

Coming to HRV, the significant relationship in this sample between higher perceived support from “the significant one” and higher SDNN HRV, gave us a first insight on the connection between psychological and physiological adjustment, perfectly mirroring what we found in literature (Porges, 2007;2008; Lutgendorf et al., 2006).

Lastly, the significant association between role functioning and SDNN HRV, could suggest how role functioning, that can be intended as the safe capability to perceive

oneself as effective in one 's own social environment, is associated with a healthier HRV.

Associations found, let us glimpse “the Great Connection” we were looking for, hence we proceeded with more strong analysis, trying to go beyond relationship, searching for causality.

What we saw for first is that the support perceived from a significant other, positively affected HRV, thus giving a causal direction to the association previously found and definitely confirming literature data (Porges, 2007;2008; Lutgendorf et al., 2006). In these women, we could suggest that the presence of a good supports activates the Social Engagement System, thus improving their HRV.

Another interesting result was the effect of higher role functioning on higher SDNN HRV. We could thus hypothesize that, in these women, perceiving themselves effective in their environment, preserving a good role functioning, positively affects their physiology, probably following the same physiological pathway, the Social Engagement System.

The second significant result, in terms of psychological-physiological integration, was that a higher value in DAS-59 full score (that is a higher presence of concerns about appearance) contributes to a higher SDNN HRV. This result was undoubtedly interesting and only apparently unusual. We could hypothesize that women with a higher DAS\_FS are prone to a better emotive disclosure, so they had better recognized their difficulties, also about body appearance concerns, more freely. Thus, this proneness to disclosure seemed to reduce emotional distress and to improve HRV, then global health (Arden-Close et al., 2013). However, this seems not to work if the disclosure happens with people outside the familiar environment; in fact, a higher referred support from friends, negatively affects HRV. Probably, this could be explained with the possible stress coming from the reiteration of facts and negative emotions that can happen when dealing with friends. Lastly, emotional avoidance can generate higher distress, thus worsening HRV.

Looking at Quality of Life as outcome, we found stimulating results.

For first, a worst perception of body appearance can negatively affect global Quality of Life. This results seems to align to previous research on other cancer sites as breast and head-neck cancer (Bergovic-Juhant et al., 2012; Nash, 2014), even if it seems to counteract with the effect that body image has on HRV. However, we can try to explain this result basing on the concept of “response fragmentation” (Pruneti, 2013): cognitive, behavioural and physiological responses are partially independent. A disclosure about body appearance concerns could improve adaptation on the physiological level. However, it could cause suffering on the cognitive level, thus worsening the perceived and referred Quality of Life.

In our sample, emerged that the use of coping strategy Fatalism, had a positive impact on global Quality of Life. This result strengthen the observation coming from correlation. In our sample, apparently counteracting literature (Classen et al., 1996; Uchida & Akechi, 2015) the most adaptive coping strategy seems to be Fatalism. Women using this strategy seemed to have a positive approach to life and to everyday difficulties deriving from their condition of cancer survivors. Thus, this strategy seemed to be effective in improving Quality of Life. Hence, we could more concretely hypothesize that Fatalism is nearer to acceptance than Fighting Spirit, as in Cotton et al., 1999, who wrote “the concept of fatalism may be much more complex. A closer look at the items that comprise the Fatalism scale reveal themes such as: taking one day at a time, counting blessings, and making the most of life”. In fact, we should interpret this scale as a “Living-a-Day” scale, mirroring thus the tendency to live a valuable present, that could explain the positive impact it has on Quality of Life.

We explored also the Emotional Functioning as outcome.

We found that a good and satisfying social support, in particular coming from one important person, seems to improve the emotional functioning in everyday life, probably making it easier to share the emotive burden caused by the disease itself and from the stigma and the fears that the disease can cause. In this important outcome, we can see again how the coping strategy that seems to work the best in emotional adjustment is fatalism. We should also remember that support coming from an important person and fatalism are in a strong relationship with each other, giving more depth to the interpretation of this interesting result.

Lastly, we conducted a specific analysis on the subsample of women who were diagnosed in reproductive age.

It is interesting to underline that DAS FS has the same negative influence in the global sample and in this subgroup. It is not surprising that women who were diagnosed earlier, have a global Quality of Life affected from the body image. However, in our sample, there is a particular trend, in fact a higher concern about sexual image seems to affect positively Quality of Life. This result could be explained, through the beneficial effect of admitting to themselves and to the partner the concerns linked to the cancer treatment and its effect on the sexual body image, , thus accepting the incoming difficulties, and perceiving a total better Quality of Life.

## CONCLUSION

In this work, we had high-ranking aims. We wanted to describe a specific portion of population and to search for a model of integration.

Certainly, the small sample in this study makes impossible to generalize the obtained results and to extend these findings to the whole population of women affected from ovarian cancer.

However, what we found, can act as a springboard for other researchers and can add, although its limitations, knowledge to this topic.

For instance, it is possible to say that the Italian sample we assessed, is halfway in cancer psychological and physiological adjustment. Surely, these women live an acceptable life as cancer survivors, but they also seem to drag concerns and difficulties, in particular linked to accepting their condition of cancer survivors. In fact, the best adjustment in these women seems to be related to the worst starting conditions: advanced cancer stage, younger age, diagnosis in reproductive age. Then, it is possible to suggest that these conditions force these women to face openly cancer and their condition of cancer survivors, pushing them “moving on” more than “trying to get back”.

This kind of analysis seems to be so important, for its immediate clinical repercussion. The women we assessed, have not ever met a clinical psychologist, thus their psychological support has been entrusted themselves, or their relatives or their doctors. Surely they did it, since none of these women seem to have a manifest psychopathology, however, we ask ourselves, what would have happened if they had met a psychologist? Maybe they would have moved more smoothly through the path of acceptance of cancer and of being a cancer survivor.

We sincerely hope that research on cancer and on cancer implications on psychological and physiological balance, could translate into wiser politics that could ensure to a cancer patient to be totally helped, not only in medical and surgical treatment but also in psychological adjustment to this huge change in the life.

Then, we wanted to find proofs of the protective “Great Connection” in these women. Again, the scarcity of our sample makes very impossible to generalize these findings to the wide population of cancer patients. However, what we found can be seen as a preliminary demonstration that this “Integrated Model of Defense” could really exist and it has to be searched in cancer survivors, in order to create applicative protocols that could effectively work on illness adjustment and Quality of Life in this population.

We found that HRV is influenced by the presence of significant figure but, in particular, we suppose that it is influenced by a proper emotive disclosure with the significant people in patients’ life. We also saw that keep functioning as a person in the personal environment reflects in a higher HRV, maybe preserving the sense of self and thus reducing distress deriving from cancer.

Hence, we can state yes to the first research question, HRV, in these women, is associated to a better psychological adjustment.

Moreover, we found in these women that Quality of Life is deeply influenced by body appearance perception, thus positively answering to our second research aim. In this sample, this is an innovative aspect because it is barely considered, since the scar they have is covered and not easily visible. However, these women, more or less consciously, see it and feel intimately hit by this scar.

Lastly, we had a huge surprise when coming to coping style. We thought that the greater positive influence on Quality of Life, would have been the fighting spirit’s one. We were wrong.

In these women, fatalism seems to be protective and to facilitate the process of cancer acceptance.

So, also according to literature, we should rephrase the concept of fatalism, as the capability to live life day-by-day, here meant as giving value to each day and to each person that shares that day. This improves social relationships and Quality of Life.

We really hope that future research could overcome the huge limits of this study as numerosity, and the use of some instruments that don't hit completely the target of what we are searching for (as Avoidance in MAC).

However, we are defining the future trajectories of this study. For first, we should increase the number of observations, recruiting women in different specialist centers in different areas of Italy.

Then, more specific instruments should be used to better assess coping avoidance, perceived support coming from doctors and sanitary staff, and general Quality of Life not linked to cancer survivorship.

It might also be interesting to see whether an intervention that improves HRV (as HRV biofeedback) could have a positive effect on emotional adjustment and Quality of Life, to get final evidences of this connection and to test new methods to effectively support cancer patients.

However, since "Rome wasn't built in a day", from this work, with all its limitations, we'll move on towards the research of an exhaustive evidence of the "Integrated Model of Defense".



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## Appendix I

### The Battery of Questionnaires

Nome \_\_\_\_\_  
Cognome \_\_\_\_\_  
Data di Nascita \_\_\_\_\_  
Comune di Residenza \_\_\_\_\_  
Email \_\_\_\_\_  
N. telefonico \_\_\_\_\_  
Data \_\_\_\_\_

#### DATI SOCIO-ANAGRAFICI

##### STATO CIVILE

Nubile/ Celibe \_ Coniugato/a \_ Convivente \_ Divorziato/ Separato/a \_  
Vedovo/a \_

FIGLI SI \_ NO \_

NUMERO DI FIGLI \_\_\_\_\_

##### SCOLARITA'

Analfabeta \_ Elementari \_ Medie \_ Superiori \_ Dipl. universitario \_ Laurea \_

##### PROFESSIONE

Eventuali modifiche dell'attività lavorativa in relazione alla malattia \_\_\_\_\_

#### CONDIZIONE MEDICA DEL PAZIENTE

Anamnesi Medico chirurgica \_\_\_\_\_

Sede della patologia \_\_\_\_\_

Breve anamnesi diagnostica \_\_\_\_\_

Familiarità di malattia \_ si \_ no \_ non sa

Specificare \_\_\_\_\_

##### *Fase attuale della malattia*

Libero da malattia \_ Tumore primario locale \_ Ripresa locale \_  
Ripresa a distanza \_ Metastatico \_ Terminale \_

##### *Fase attuale della terapia*

In attesa di diagnosi \_ In attesa di trattamento \_ In trattamento \_  
Terapia supportava \_ Cure palliative \_ Follow up \_

##### *Trattamenti effettuati negli ultimi 3 mesi*

Chemioterapia \_ Radioterapia \_ Ormonoterapia \_  
Op. chirurgica effettuata (circa) \_\_\_\_\_ Terapia metabolica \_

#### VALUTAZIONE PSICONCOLOGICA

Visite psicologiche e/o psichiatriche pre-esistenti alla patologia oncologica

si \_ no \_

Eventuali diagnosi \_\_\_\_\_ Terapia \_\_\_\_\_

##### *Condizione attuale*

Assunzione di psicofarmaci Si \_ No \_ se si, specificare

Trattamenti psicoterapeutici Si \_ No \_

Se si specificare l'orientamento teorico \_\_\_\_\_

Problema attuale riferito dal paziente \_\_\_\_\_

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## VALUTAZIONE DEL SUPPORTO SOCIALE PERCEPITO

Scala multidimensionale del supporto sociale percepito (Zimet, Dahlen, Zimet e Farley 1998)

AFFERMAZIONE	Moltissimo in <b>disaccordo</b>	Molto in disaccordo	In <b>disaccordo</b>	Neutro	<b>D'accordo</b>	Molto <b>d'accordo</b>	Moltissimo <b>d'accordo</b>
<b>1.</b> C'è una persona in particolare che mi è vicina quando ho bisogno	1	2	3	4	5	6	7
<b>2.</b> C'è una persona in particolare con cui posso condividere gioie e dolori	1	2	3	4	5	6	7
<b>3.</b> La mia famiglia si dà molto da fare per aiutarmi	1	2	3	4	5	6	7
<b>4.</b> Ho l'aiuto e il supporto emotivo di cui ho bisogno dalla mia famiglia	1	2	3	4	5	6	7
<b>5.</b> Ho una persona in particolare che è fonte reale di conforto per me	1	2	3	4	5	6	7
<b>6.</b> I miei amici si danno da fare per aiutarmi	1	2	3	4	5	6	7
<b>7.</b> Posso contare sui miei amici quando le cose vanno male	1	2	3	4	5	6	7
<b>8.</b> Posso parlare dei miei problemi con la mia famiglia	1	2	3	4	5	6	7
<b>9.</b> Ho amici con cui posso condividere le mie gioie e i miei dolori	1	2	3	4	5	6	7
<b>10.</b> C'è una persona in particolare nella mia vita cui importa di come mi sento	1	2	3	4	5	6	7
<b>11.</b> La mia famiglia mi aiuta a prendere decisioni	1	2	3	4	5	6	7
<b>12.</b> Posso parlare dei miei problemi con i miei amici	1	2	3	4	5	6	7



## THE DERRIFORD APPEARANCE SCALE (DAS-59)

### Questo questionario riguarda il tuo rapporto con il tuo aspetto fisico

La prima parte del questionario è predisposta per scoprire se sei sensibile o consapevole di una qualche caratteristica del tuo aspetto fisico (anche se di solito non è visibile agli altri).

(a) C'è una qualche peculiarità del tuo aspetto fisico (per quanto piccola) rispetto alla quale sei sensibile? Sì / No

Se la risposta è **no**, vai direttamente alla Parte 2,  
Se la risposta è **sì**, continua di seguito:

(b) Il tratto del mio aspetto fisico del quale mi preoccupo di più è  
.....  
.....

**Da adesso in poi ci riferiremo a questo tratto del tuo aspetto fisico denominandolo "caratteristica"**

(c) Ciò che non mi piace della mia "caratteristica" è  
.....  
.....  
.....

(d) Se sei suscettibile o preoccupato di altre "caratteristiche" del tuo corpo o del tuo aspetto fisico, elencale qui di seguito.....  
.....  
.....

## PARTE 2

Leggi attentamente le seguenti affermazioni e poi fai un cerchio intorno al numero sulla destra corrispondente alla risposta che ti sembra più appropriata. Se nessuna descrizione è adeguata alla tua situazione fai un cerchio attorno ad N/A.

**Assicurati di rispondere a tutte le domande e di non tralasciare nessun elemento.**

(1 quasi mai, 2 a volte, 3 spesso, 4 quasi sempre, N/A Non Applicabile)

- |   |   |   |   |   |     |
|---|---|---|---|---|-----|
| 1 Sono consapevole della mia "caratteristica" ..... | 1 | 2 | 3 | 4 | N/A |
| 2 Evito i bambini per strada .....                  | 1 | 2 | 3 | 4 | N/A |
| 3 Faccio amicizia con difficoltà .....              | 1 | 2 | 3 | 4 | N/A |

- 4 Evito di svestirmi di fronte al mio coniuge/partner .....1 2 3 4 N/A  
 5 Per il momento cerco di evitare di recarmi a scuola/università/lavoro ..1 2 3 4  
 N/A  
 6 Evito di andare in locali pubblici/ristoranti .....1 2 3 4 N/A  
 7 Evito di andare alle feste/ in discoteca .....1 2 3 4 N/A  
 8 Presto particolare attenzione a come appaiono le "caratteristiche" degli altri ....1  
 2 3 4 N/A  
 9 Evito gli spogliatoi in comune .....1 2 3 4 N/A  
 10 Evito di farmi fotografare .....1 2 3 4 N/A  
 11 Evito che mi si bagnino i capelli .....1 2 3 4 N/A  
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- 12 Sono stato ferito dai commenti altrui circa la mia "caratteristica"....1 2 3 4 N/A  
 13 Evito di fare acquisti nei grandi magazzini .....1 2 3 4 N/A  
 14 Evito di uscire di casa .....1 2 3 4 N/A  
 15 Introduco nella conversazione la mia "caratteristica" prima che lo facciano gli  
 altri.....1 2 3 4 N/A  
 16 Mi chiudo nel mio guscio .....1 2 3 4 N/A  
 17 La mia consapevolezza mi rende scontroso a casa .....1 2 3 4 N/A  
 18 Gli altri mi giudicano male a causa del mia "caratteristica" .....1 2 3 4 N/A  
 19 In passato cercavo di evitare di recarmi a scuola/università/lavoro .....1  
 2 3 4 N/A  
 20 Mi sento a disagio con i miei amici .....1 2 3 4 N/A  
 21 Mi sento un mostro .....1 2 3 4 N/A  
 22 Mi preoccupa per il mio equilibrio mentale .....1 2 3 4 N/A  
 23 La mia consapevolezza ha una ricaduta negativa sulla mia vita sessuale .....1 2  
 3 4 N/A  
 24 La mia consapevolezza ha una ricaduta negativa sul mio matrimonio .....1 2  
 3 4 N/A  
 25 La mia "caratteristica" mi provoca dolore/disagio .....1 2 3 4 N/A  
 26 La mia "caratteristica" mi impedisce di fare le cose che vorrei .....1 2 3 4 N/A  
 27 La mia "caratteristica" mi fa sentire non attraente .....1 2 3 4 N/A  
 28 La mia "caratteristica" mi fa sentire non desiderabile .....1 2 3 4 N/A  
 29 La mia "caratteristica" mi fa sentire isolato .....1 2 3 4 N/A  
 30 La mia "caratteristica" mi fa sentire a disagio .....1 2 3 4 N/A  
 31 La mia "caratteristica" mi fa sentire inferiore .....1 2 3 4 N/A  
 32 La mia "caratteristica" mi fa sentire respinto .....1 2 3 4 N/A  
 33 La mia "caratteristica" mi fa sentire inutile .....1 2 3 4 N/A

**QUANTO TI SENTI A DISAGIO QUANDO:**

- (1-2 per nulla/3-4 moderatamente/5 estremamente a disagio N/A non applicabile)  
 34 Altre persone fissano la tua "caratteristica" .....1 2 3 4 5 N/A

- 35 Altre persone fanno osservazioni sulla tua “caratteristica” .....1 2 3 4 5 N/A  
36 Altre persone fanno domande sulla tua “caratteristica” .....1 2 3 4 5 N/A  
37 Vai a mare .....1 2 3 4 5 N/A  
38 Gli altri ti osservano da una particolare angolazione (es di fronte , di profilo)  
.....1 2 3 4 5 N/A  
39 Vai a scuola/ università/ lavoro .....1 2 3 4 5 N/A  
40 Vai sui mezzi pubblici .....1 2 3 4 5 N/A  
41 Ti guardi allo specchio /alla finestra .....1 2 3 4 5 N/A  
42 Incontri persone che non conosci .....1 2 3 4 5 N/A  
**QUANTO TI INFASTIDISCE:**  
43 Non poter indossare i tuoi abiti preferiti .....1 2 3 4 5 N/A  
44 Non poter cambiare il tuo taglio di capelli .....1 2 3 4 5 N/A  
45 Non poter andare a nuotare .....1 2 3 4 5 N/A  
46 Non poter praticare le attività sportive .....1 2 3 4 5 N/A  
47 Non essere in grado di avere una vita sociale .....1 2 3 4 5 N/A  
48 Non essere in grado di rispondere a chi suona alla porta.....1 2 3 4 5 N/A  
49 Non essere in grado di guardarti allo specchio .....1 2 3 4 5 N/A  
50 Non essere in grado di andare in locali pubblici/ristoranti .....1 2 3 4 5 N/A  
51 Non essere in grado di uscire di casa nelle giornate ventose .....1 2 3 4 5 N/A  
**IN GENERALE:**  
(1 per nulla/2 poco /3 moderatamente/4 abbastanza/ 5 estremamente N/A Non Applicabile)  
52 Quanto ti senti sicuro di te? .....1 2 3 4 5 N/A  
53 Quanto ti senti irritabile? .....1 2 3 4 5 N/A  
54 Quanto ti senti sicuro? .....1 2 3 4 5 N/A  
55 Quanto ti senti allegro? .....1 2 3 4 5 N/A  
56 Quanto ti senti normale? .....1 2 3 4 5 N/A  
57 Quanto ti senti femminile/maschile? .....1 2 3 4 5 N/A  
58 Quanto ti senti sofferente? .....1 2 3 4 5 N/A  
59 Quanto ti senti ostile? .....1 2 3 4 5 N/A



## Scala MAC sugli Stili di Coping

**1= COMPLETAMENTE IN DISACCORDO, NON E' PER NULLA IL MIO CASO**

**2= IN DISACCORDO, NON E' IL MIO CASO**

**3= D'ACCORDO, E' IL MIO CASO**

**4= COMPLETAMENTE D'ACCORDO, E' ESATTAMENTE IL MIO CASO**

- |  |                |
|--|----------------|
| 1. Sto facendo cose che penso miglioreranno la mia salute<br>(ad esempio ho cambiato abitudini alimentari)               | <b>1 2 3 4</b> |
| 2. Sento che non posso fare niente per tirarmi su  | <b>1 2 3 4</b> |
| 3. Sento che i problemi di salute mi impediscono di guardare avanti  | <b>1 2 3 4</b> |
| 4. Penso che il mio atteggiamento positivo favorirà la mia salute  | <b>1 2 3 4</b> |
| 5. Non sto a pensare troppo alla malattia  | <b>1 2 3 4</b> |
| 6. Credo fermamente che starò meglio   | <b>1 2 3 4</b> |
| 7. Sento che niente di ciò che posso fare conterà qualcosa   | <b>1 2 3 4</b> |
| 8. Ho lasciato tutto nelle mani dei dottori  | <b>1 2 3 4</b> |
| 9. Sento che la vita è senza speranza  | <b>1 2 3 4</b> |
| 10. Sto facendo cose che penso miglioreranno la mia salute<br>(ad esempio esercizio fisico)                              | <b>1 2 3 4</b> |
| 11. Da quando mi è stata diagnosticata questa malattia ho capito<br>quanto sia preziosa la vita e cerco di approfittarne | <b>1 2 3 4</b> |
| 12. Mi sono messo/a nelle mani di Dio  | <b>1 2 3 4</b> |
| 13. Ho progetti per il futuro (ad es. vacanze, lavoro, casa, famiglia)   | <b>1 2 3 4</b> |
| 14. Ho paura che il tumore ricompaia o si aggravi  | <b>1 2 3 4</b> |

15. Ho avuto una buona vita, tutto quel che resta-ogni giorno è guadagnato **1 2 3 4**
16. Penso che il mio stato d'animo possa avere grande importanza per la mia salute **1 2 3 4**
17. Sento che non c'è nulla che posso fare per aiutarmi **1 2 3 4**
18. Cerco di andare avanti come ho sempre fatto **1 2 3 4**
19. Mi piacerebbe prendere contatti con persone che sono nella mia stessa barca **1 2 3 4**
20. Sono determinato/a a buttare tutto dietro le spalle **1 2 3 4**
21. Mi è difficile credere che questo sia capitato a me **1 2 3 4**
22. Mi sento molto in ansia per la mia malattia **1 2 3 4**
23. Non ho molta speranza per il futuro **1 2 3 4**
24. Per ora vivo alla giornata **1 2 3 4**
25. Ho voglia di lasciar perdere tutto **1 2 3 4**
26. Cerco di scherzarci o ironizzarci sopra **1 2 3 4**
27. Altre persone si preoccupano per me più di quanto non mi preoccupi io **1 2 3 4**
28. Penso a chi sta peggio di me **1 2 3 4**
29. Sto tentando di raccogliere più informazioni che posso sulla mia malattia **1 2 3 4**
30. Sento che non riesco a controllare ciò che sta accadendo **1 2 3 4**
31. Cerco di avere un atteggiamento molto positivo **1 2 3 4**

- |  |                |
|--|----------------|
| 32. Mi tengo occupato/a così da non aver tempo per pensarci su | <b>1 2 3 4</b> |
| 33. Evito di scoprire o sapere cose sulla mia malattia         | <b>1 2 3 4</b> |
| 34. Vedo la mia malattia come una sfida                        | <b>1 2 3 4</b> |
| 35. Sono fatalista a riguardo. Sarà quel che sarà              | <b>1 2 3 4</b> |
| 36. Mi sento completamente perduto/a su cosa fare              | <b>1 2 3 4</b> |
| 37. Mi sento molto arrabbiato/a per quello che mi è capitato   | <b>1 2 3 4</b> |
| 38. Non credo davvero di essere stato ammalato/a               | <b>1 2 3 4</b> |
| 39. Tengo conto di ciò che ho di buono                         | <b>1 2 3 4</b> |
| 40. Tento di combattere la mia malattia                        | <b>1 2 3 4</b> |



## **EORTC QLQ-C30 (version 3.0)**

**1-No; 2 - Un po'; 3- Parecchio; 4- Moltissimo**

1. Ha difficoltà nel fare lavori faticosi, come sollevare una borsa della spesa pesante o una valigia? **1 2 3 4**
2. Ha difficoltà nel fare una lunga passeggiata? **1 2 3 4**
3. Ha difficoltà nel fare una breve passeggiata fuori casa? **1 2 3 4**
4. Ha bisogno di stare a letto o su una sedia durante il giorno? **1 2 3 4**
5. Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno? **1 2 3 4**

### **Durante gli ultimi sette giorni:**

**1-No; 2-Un po'; 3-Parecchio; 4- Moltissimo**

6. Ha avuto limitazioni nel fare il Suo lavoro o i lavori di casa? **1 2 3 4**
7. Ha avuto limitazioni nel praticare i Suoi passatempi, hobby o altre attività di divertimento o svago? **1 2 3 4**
8. Le è mancato il fiato? **1 2 3 4**
9. Ha avuto dolore? **1 2 3 4**
10. Ha avuto bisogno di riposo? **1 2 3 4**
11. Ha avuto difficoltà a dormire? **1 2 3 4**
12. Ha sentito debolezza? **1 2 3 4**
13. Le è mancato l'appetito? **1 2 3 4**
14. Ha avuto un senso di nausea? **1 2 3 4**
15. Ha vomitato? **1 2 3 4**

### **Durante gli ultimi sette giorni:**

**1-No; 2-Un po'; 3-Parecchio; 4- Moltissimo**

16. Ha avuto problemi di stitichezza? **1 2 3 4**
17. Ha avuto problemi di diarrea? **1 2 3 4**
18. Ha sentito stanchezza? **1 2 3 4**
19. Il dolore ha interferito con le Sue attività quotidiane? **1 2 3 4**
20. Ha avuto difficoltà a concentrarsi su cose come leggere un giornale o guardare la televisione? **1 2 3 4**
21. Si è sentito(a) teso(a)? **1 2 3 4**
22. Ha avuto preoccupazioni? **1 2 3 4**
23. Ha avuto manifestazioni di irritabilità? **1 2 3 4**
24. Ha avvertito uno stato di depressione? **1 2 3 4**
25. Ha avuto difficoltà a ricordare le cose? **1 2 3 4**
26. Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con la Sua vita familiare? **1 2 3 4**
27. Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con le Sue attività sociali? **1 2 3 4**
28. Le Sue condizioni fisiche o il Suo trattamento medico Le hanno causato difficoltà finanziarie? **1 2 3 4**

**Per le seguenti domande ponga un cerchio intorno al numero da 1 a 7 che meglio**

**corrisponde alla Sua risposta:**

29. Come valterebbe in generale la Sua salute durante gli ultimi sette giorni?

1 2 3 4 5 6 7

1= Pessima; 7=Ottima

30. Come valuterebbe in generale la Sua qualità di vita durante gli ultimi sette giorni?

1 2 3 4 5 6 7

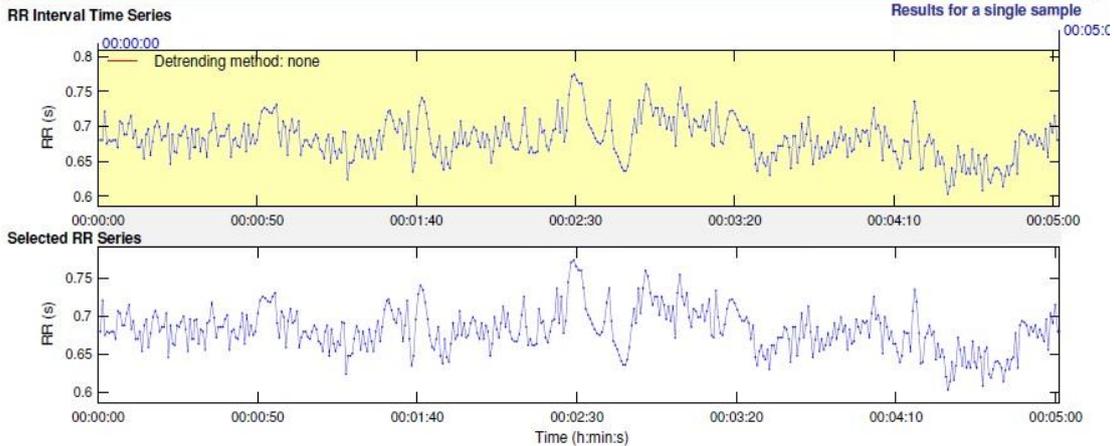
1=Pessima; 7=Ottima

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# Appendix II

## Kubios Analysis Results

### HRV Analysis Results



#### Time-Domain Results

Variable	Units	Value
Mean RR*	(ms)	681.6
STD RR (SDNN)	(ms)	28.2
Mean HR*	(1/min)	86.17
STD HR	(1/min)	3.64
RMSSD	(ms)	22.3
NN50	(count)	8
pNN50	(%)	1.8
RR triangular index		7.754
TINN	(ms)	130.0

#### Distributions\*

#### Frequency-Domain Results

**FFT spectrum** (Welch's periodogram: 256 s window with 50% overlap)

Frequency Band	Peak (Hz)	Power (ms <sup>2</sup> )	Power (%)	Power (n.u.)
VLF (0-0.04 Hz)	0.0039	365	44.1	
LF (0.04-0.15 Hz)	0.0430	299	36.0	64.4
HF (0.15-0.4 Hz)	0.1836	164	19.8	35.5
Total		829		
LF/HF		1.817		

**AR Spectrum** (AR model order = 16, not factorized)

Frequency Band	Peak (Hz)	Power (ms <sup>2</sup> )	Power (%)	Power (n.u.)
VLF (0-0.04 Hz)	0.0039	368	52.9	
LF (0.04-0.15 Hz)	0.0430	201	29.0	61.6
HF (0.15-0.4 Hz)	0.1523	125	17.9	38.1
Total		694		
LF/HF		1.615		

#### Nonlinear Results

Variable	Units	Value
<b>Poincare plot</b>		
SD1	(ms)	15.8
SD2	(ms)	36.7
<b>Recurrence plot</b>		
Mean line length (Lmean)	(beats)	10.13
Max line length (Lmax)	(beats)	104
Recurrence rate (REC)	(%)	32.39
Determinism (DET)	(%)	97.57
Shannon Entropy (ShanEn)		3.123
<b>Other</b>		
Approximate entropy (ApEn)		1.275
Sample entropy (SampEn)		1.795
Detrended fluctuations (DFA): $\alpha_1$		1.034
Detrended fluctuations (DFA): $\alpha_2$		0.957
Correlation dimension (D2)		0.572
Multiscale entropy (MSE)		0.882 - 2.316

#### Poincare Plot

#### Detrended fluctuations (DFA)

\*Results are calculated from the non-detrended selected RR series.



**Appendix III**  
Informed Consent Document



# UNIVERSITÀ DEGLI STUDI DI PARMA

DIPARTIMENTO DI MEDICINA CLINICA E SPERIMENTALE

Via A. Gramsci, 14 - 43126 Parma - Italia

**Responsabile del progetto: Prof. Carlo Pruneti, Dott.ssa Chiara Cosentino**

**MODULO DI CONSENSO INFORMATO PER LA PARTECIPAZIONE  
ALLO STUDIO DAL TITOLO:**

**Lo sento nel Cuore**

Valutazione della Correlazione tra adattamento emotivo e sociale e variabilità della  
frequenza cardiaca in donne con cancro ovarico

Prima di decidere liberamente se vuole partecipare a questo studio, **LEGGA  
ATTENTAMENTE** questo consenso informato e ponga al responsabile della ricerca  
tutte le domande che riterrà opportune al fine di essere pienamente informato degli  
scopi, delle modalità di esecuzione dell'esperimento e dei possibili inconvenienti  
connessi.

La preghiamo di ricordare che questo è un progetto di ricerca e che la sua  
partecipazione è completamente volontaria. Lei si potrà ritirare in qualunque  
momento.

## **SCOPO DELLO STUDIO**

La ricerca ha lo scopo di valutare le relazioni presenti tra l'adattamento emotivo e sociale alla patologia oncologica e la variabilità della frequenza cardiaca, indice di funzionalità e di equilibrio neurovegetativo.

## **STRUMENTI UTILIZZATI**

DAS-59 : questionario per la valutazione dell'immagine corporea;

MSPSS: questionario per la valutazione della percezione del supporto sociale;

MAC: questionario per la valutazione degli stili di fronteggiamento della patologia oncologica;

EORTC-QLQ 30: questionario per la valutazione della qualità della vita;

emWave (HeartMath): per la registrazione a breve termine della variabilità della frequenza cardiaca.

## **PROCEDURA SPERIMENTALE**

Ogni soggetto verrà sottoposto a valutazione basale dell'adattamento emotivo e sociale alla patologia; verrà, quindi, registrata la variabilità della frequenza cardiaca a breve termine (5 minuti).

## **ALTRE INFORMAZIONI UTILI**

**Riservatezza.** I dati raccolti saranno trattati in accordo con le leggi sulla privacy e in conformità al Decreto Legislativo 30 giugno 2003 n. 196 "Codice in materia di protezione dei dati personali", garantendo l'anonimato dei partecipanti.

Le ricordiamo che in caso lei abbia bisogno di delucidazioni su qualunque aspetto della procedura sperimentale, il responsabile della ricerca, e i suoi collaboratori, sono a Sua completa disposizione.

**Compili la parte seguente:**

Il/la sottoscritto/a \_\_\_\_\_

Nato/a il \_\_\_\_\_

Dichiara:

- di aver letto attentamente le spiegazioni relative a questo studio e l'intera procedura sperimentale;
- di essere stato informato/a riguardo alle finalità e agli obiettivi della ricerca in questione;
- di aver avuto la possibilità di porre domande a proposito di qualsiasi aspetto della procedura sperimentale e di aver ottenuto risposte soddisfacenti;
- di essere a conoscenza dei disagi dell'esperimento;
- di aver ricevuto soddisfacenti assicurazioni sulla riservatezza delle informazioni ottenute dall'esame della propria persona;
- di essere consapevole di potersi ritirare in qualsiasi fase dello studio;
- di aver liberamente dato il consenso alla partecipazione a questo studio.

Data \_\_\_\_\_

Firma del partecipante: \_\_\_\_\_



## *Acknowledgments*

Grazie a chi mi ha insegnato a fare domande;

Grazie a chi mi sprona a fare domande;

Grazie a chi con un abbraccio mi accoglie, quando mi faccio troppe domande.